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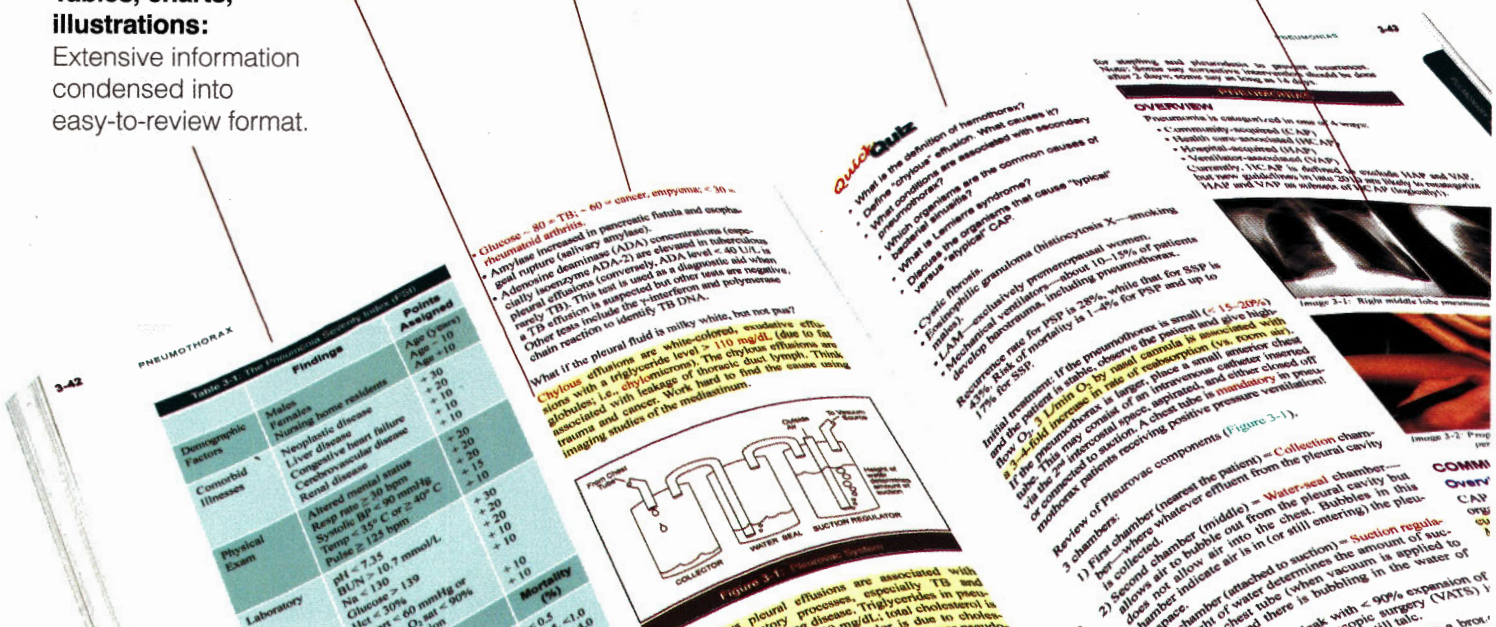

MedStudy®

INTERNAL MEDICINE REVIEW

CORE CURRICULUM

15th EDITION

Book 3 of 5

Topics in this volume:

Cardiology

Rheumatology

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with Candace L. Walkley, MD and J. Thomas Cross, Jr., MD, MPH, FACP

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CORE CURRICULUM

15th EDITION

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with J. Thomas Cross, Jr., MD, MPH, FACP

CARDIOLOGY

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Cardiology

The Electrocardiogram

PROCEDURES, LABS, PHYSICAL EXAM

CHEST X-RAYS

Know all the following chest x-ray findings!

Chest x-ray is an effective means of quickly determining significant increases in both overall heart size and (sometimes) heart chamber sizes. A cardiothoracic ratio > 50% indicates an enlarged cardiac silhouette, suggesting either cardiomegaly or a pericardial effusion. This is the ratio comparing the most rightward and leftward borders of the heart seen on a posteroanterior (PA) chest x-ray, divided by the transverse chest diameter (measured from the inside rib margin at the widest point above the costophrenic angles on a PA chest film). This ratio is valid only for an upright, non-rotated film on full inspiration (diaphragm fully contracted) with a well-visualized cardiac outline and when there is no abdominal compression on the diaphragm, such as that caused by ascites or pregnancy.

On the PA film, the left ventricle causes the bulge in the left-lower side of the cardiac shadow; the right atrium (RA) causes the outline on the right; and the area of the cardiac "waistline"—between the aortic knob and the left ventricle (LV)—is formed by the main pulmonary artery and the left atrial (LA) appendage (Image 5-1).

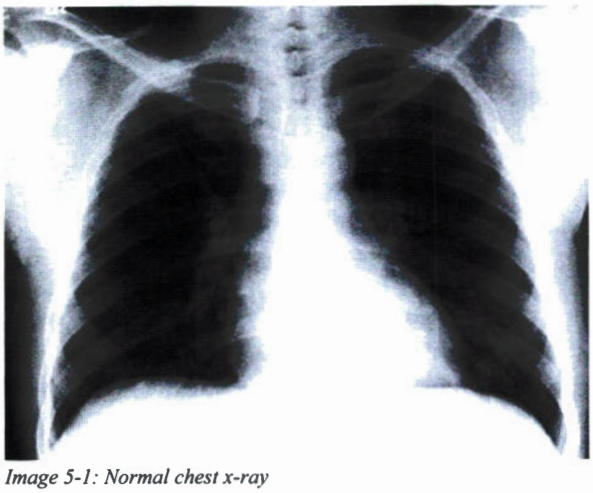


Image 5-1: Normal chest x-ray

On the lateral view, any increase in the mass of the left ventricle extends the cardiac shadow posteriorly and lower—closer to the diaphragm. Any increase in the mass of the right ventricle fills in the lower part of the anterior clear space behind the sternum.

Coarctation of the aorta (COA) is indicated by absence of a normal aortic arch. Instead, you may see the "3" sign, which is created by a prominent, left subclavian artery, the coarctation, and post-stenotic dilation of the descending aorta. The barium swallow may show a "reversed 3," due to the impressions of the arterial structures on the esophagus. Adults also show intercostal rib notching due to collateral flow through tortuous intercostal arteries.

Image 5-2: "Water bottle" heart

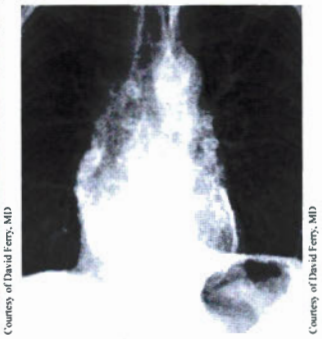


Image 5-3: Pericardial calcification

Congestive heart failure (CHF) is indicated by cardiomegaly, pulmonary vascular redistribution (with visibly thickened upper lobe pulmonary veins), Kerley B lines, and pleural effusions (usually right > left).

An anomalous pulmonary vein that drains into the inferior vena cava may create a "scimitar sign" on chest x-ray. This is a curvilinear opacity in the right lower lung field due to associated lung hypoplasia.

Aortic abnormalities that you may see include tortuosity and calcification. An aortic aneurysm is sometimes easily visible on the lateral film. An aortic dissection may show up as mediastinal widening on the PA projection.

Pericardial effusion is suggested by a "water bottle" or a "water balloon" shape to the heart, sometimes with significant enlargement of the cardiac silhouette (Image 5-2).

"Shunt vascularity" is visible with significant ventricular septal defect (VSD), atrial septal defect (ASD), or other left-to-right shunts.

Areas of calcifications on chest x-ray:

- Aortic: Think dissection if you see a separation between calcification and the aortic border, especially if the mediastinum appears wide.
- Myocardial: usually from an apical aneurysm.
- Valvular: usually aortic.
- Annular (ring-shaped): mitral annular calcification; if it is a perfect ring then a prosthetic valve is likely (especially if surgical clips are also present).
- Pericardial: Think constrictive pericarditis; or think TB if the clinical history suggests significant exposure (Image 5-3).

Know that a single lead in the apex of the RV indicates the presence of an electronic ventricular pacemaker or implanted defibrillator, 2 leads indicate an AV sequential (dual-chamber) pacemaker, and 3 leads indicate a biventricular pacemaker.

ECHO

Echocardiography is an ultrasound modality used to image the heart. It utilizes M-mode and 2D for structural imaging and Doppler for assessing blood flow rate and direction.

Best use of echo is for the following scenarios:

- Right and left ventricular structure and systolic function
- Valvular heart disease (stenosis, regurgitation, mitral valve prolapse and other structural abnormalities, endocarditis, prosthetic valves)
- Congenital heart disease (VSD, ASD, the numerous cyanotic heart diseases)
- Ischemic heart disease and myocardial infarction (including post-MI complications)
- Cardiomyopathy (including hypertrophic cardiomyopathy)
- Pericardial disease
- Cardiac masses (myxoma, thrombus)
- Diseases of the aorta and pulmonary artery
- Evaluation of left ventricular hypertrophy
- Diastolic function
- Cardiac sources of emboli

Transesophageal echocardiogram (TEE) is an echo performed with an esophageal probe. It offers higher-resolution images compared to transthoracic imaging and is especially useful for evaluating:

- Valvular structure and function
- Left atrium
- Intracardiac masses and thrombi
- Intracardiac shunts
- Endocarditis
- Aortic dissection
- Ventricular function

A bubble study is performed by injecting hand-agitated saline and air into the venous system; it is also used to evaluate intracardiac shunts.

In a cancer patient with progressive dyspnea, think of pericardial effusion/tamponade.

Doppler echocardiography measures the velocity and direction of the blood flow. Doppler echo determines mean gradients, peak velocities, and valve area. So, it is useful in determining the severity of valvular stenosis or regurgitation, as well as in evaluating left ventricular diastolic function, left ventricular outflow tract gradients, and intracardiac shunts. It is also helpful in estimating pulmonary pressure.

Doppler echo is also an effective, quick way to check an acutely deteriorating post-MI patient for ventricular septal rupture and mitral regurgitation due to papillary muscle dysfunction.

Advances in technology have led to production of small, handheld echocardiography devices that can be carried to the bedside. Their actual utility is still being determined.

CARDIAC STRESS TESTS

Overview

The increased demand for myocardial oxygen with exercise is the key factor in the use of exercise testing as a diagnostic tool for coronary artery disease (CAD), also known as coronary heart disease (CHD). Hemodynamic data such as heart rate, blood pressure, and exercise capacity are important features of the exercise test. There are 2 general types of cardiac stress tests done:

1) Exercise treadmill test (ETT; basic treadmill testing without imaging)
2) Stress imaging testing (The "stress" may be exercise or pharmacologic stress.) These include:
   - Echo stress testing (or "stress echo")
   - Myocardial perfusion imaging (MPI)

A patient's pretest probability of coronary artery disease must be taken into account to determine the utility of performing one of these tests. (A positive test in a low-risk patient is more likely to be a false positive, and a negative test in a high-risk patient is more likely to be a false negative.)

Exercise Treadmill Test (Without Imaging)

Exercise treadmill test (ETT) is useful for testing for ischemia and functional capacity, and for determining prognosis (including post-MI). It has the lowest sensitivity and specificity of the stress tests—but is quite sensitive and specific if pretest probability of coronary artery disease (CAD) is taken into account. The patient typically exercises on a treadmill using standard exercise protocols, such as the Bruce protocol (see Table 5-4 on page 5-10). The level of maximal exercise achieved on the ETT is measured in metabolic equivalents (METS).

ETT is typically included in the initial evaluation of suspected ischemic heart disease and is done as a prognostic indicator after MI.

ETT is not good for localizing ischemia or determining myocardial viability. It is also not as useful if the patient is unable to perform sufficiently on the treadmill (must meet 85% of age-predicted maximum heart rate), or if the patient has baseline ECG abnormalities that may interfere with reading the results (e.g., LVH, LBBB, WPW, ventricular pacing, and resting ST changes), or is on digoxin.

Know the following information related to ETTs:

Definition of a positive ETT: flat or down-sloping ST-segment depression > 1 mm and occurring 80 msec following the J-point in at least 3 contiguous leads.

Unlike ST elevation, ST depression does not correlate with the anatomic location of ischemia.

The more inferior the ST depression is, the less specificity for ischemia, whereas the more lateral, the more specificity. For example, exercise-induced isolated inferior ST depression including lead II is of little value

QuickQuiz

- On a lateral view CXR, extension of the heart border posteriorly and inferiorly indicates enlargement of which ventricle?
- On a lateral view CXR, extension of the cardiac shadow of the lower part of the anterior clear space behind the sternum indicates enlargement of which ventricle?
- What conditions is a TEE useful for evaluating?
- When are stress imaging studies done instead of an exercise treadmill test?

(specificity 44%). On the other hand, ST depression in leads including V5 is much more specific (84%).

ST elevation during an ETT in 3 contiguous leads is also considered positive but is much less commonly seen.

Reasons for discontinuing the ETT:

- ST-segment depression > 2 mm,
- decrease in systolic BP > 15 mmHg,
- development of ventricular tachycardia,
- development of severe chest pain,
- shortness of breath, or
- lightheadedness.

Note: Achieving target heart rate alone is not a reason to discontinue the ETT.

False-positive rate is 15–20% overall (higher in women, highest in isolated inferior ST depression); false-negative rate is 20–30%. Per the Bayesian theorem, this means that the patient's prior probability of heart disease (i.e., number of risk factors, clinical history) has a significant effect on the predictive value of the test. False positives are also higher in those taking beta-blockers or who are unable to achieve the target heart rate.

Excellent exercise tolerance (> 10 METS) is associated with a good prognosis independent of the degree of coronary artery disease.

Note: Coronary artery spasm is the probable cause of transient and reversible ST-segment elevation on the ETT.

Stress Imaging Tests

Overview

The stress imaging studies are the stress echo and myocardial perfusion imaging (MPI). The choice of which one to use is often based on operator experience at the facility.

Use these stress imaging studies when you need to determine the region and amount of ischemia, measure ejection fraction (EF), and/or assess for myocardial viability. You can also use them as the initial diagnostic method if a higher false positivity is expected with ETT (see on page 5-2). Stress imaging studies have greater sensitivity and specificity than the regular ETT.

Stress-related decreases in ejection fraction and transient ischemic dilation indicate the presence of severe ischemia or multivessel disease.

Stressing the Heart for Imaging Studies

The "stress" portion of these tests can be performed with exercise or pharmacologic agents.

With **exercise**, imaging studies are done just like an ETT and require the same ability to meet 85% of age-predicted maximum heart rate. Exercise is preferable because it provides additional functional and prognostic information. Exercise is not used in patients with pacemakers or LBBB.

The **pharmacologic agent** used for cardiac imaging studies is dobutamine or one of several vasodilators.

Dobutamine is both inotropic + chronotropic and causes the heart to act as it normally responds to exercise. As with exercise, dobutamine is not used in patients with pacemakers but dobutamine stress echo is fine for LBBB (not dobutamine MPI). Dobutamine is the typical agent used for stress echo and for MPI in those with contraindications to vasodilators (especially bronchospasm).

Adenosine, dipyridamole, and regadenoson are the vasodilators used in the pharmacologic stress tests. These vasodilators work in this setting by dilating and increasing blood flow in normal cardiac vessels while doing little to change the flow in stenotic vessels. The dilated normal vessels steal flow from the stenotic vessels causing perfusion defects in scans (and ST segment changes in ECGs).

Activation of the adenosine A2A receptor causes this vasodilation; but adenosine and dipyridamole nonselectively activate the other adenosine receptors (A1, A2B, and A3), and A2B receptor activation causes bronchospasm. Regadenoson is a more selective A2A receptor activator and has less bronchospasm effect. Regadenoson has been used successfully in small trials in patients with non-severe bronchospasm, but larger studies are needed to validate these results; thus, for Boards, dobutamine is the pharmacologic agent of choice for patients with a history of bronchospasm.

Stress Echo and MPI Indications

Unlike ETT, exercise stress echo and MPI can be used in patients:

- with resting ECG ST changes,
- with Wolff-Parkinson-White (WPW) syndrome, or
- on digoxin therapy.

Note that it is a common misconception that these patients require chemical stress, but this is definitely not true! If they can exercise, these patients have a class I

indication for a stress echo with exercise or MPI with exercise (i.e., these patients need the imaging, not the chemical stress).

On the other hand, MPI with vasodilators (not exercise or dobutamine!) is the test of choice for patients with left bundle-branch block (LBBB) or paced ventricular rhythm.

In certain circumstances, these imaging scans are done with different protocols than those used to detect ischemia. For instance, they may be done after an MI to determine the severity of myocardial scarring or the viability of the myocardium (i.e., will revascularization work?). Or, in the case of an abnormal EF, low-dose dobutamine echo may be used to determine the degree of aortic stenosis or the severity of hypertrophic obstructive cardiomyopathy.

Stress Echo

The stress echo is a widely used test for myocardial ischemia. It is less expensive and just as accurate as MPI (next).

Use exercise or, if unable to exercise, use dobutamine to achieve target heart rate. Then take echo images to evaluate changes in wall motion and systolic ejection fraction with stress. Abnormal wall motion suggests ischemia of that region of the myocardium.

Vasodilators are not used for stress echo.

Myocardial Perfusion Imaging (MPI)

These stress tests use radioisotopes with single-photon emission computed tomography (SPECT). The agents are IV thallium-201 (^{201}Tl) or IV technetium-99m (^{99m}Tc)–labeled substances (usually sestamibi or tetrofosmin).

These tracers distribute in heart tissue in proportion to blood flow; this distribution is recorded by a gamma camera. After injection at the peak of stress, ischemic areas take up less radionuclide than surrounding tissues but will show normal distribution at rest some time (hours) later ("reversible"). Areas that show underperfusion, both during exercise and at rest ("fixed"), are areas of infarction.

MPI is often done with ECG-synchronized "gated" technique, where multiple images are combined and smoothed for better resolution. This allows for assessment of wall motion and ventricular size and function (estimates ejection fraction).

Target heart rate must be achieved with exercise or dobutamine for an adequate test; however, achievement of target heart rate is not needed with vasodilator stress. MPI using vasodilator stress tends to be more sensitive and specific than dobutamine, but either is acceptable.

Cardiac positron emission tomography (PET) and cardiac MRI are also used in some circumstances to assess for myocardial ischemia and viability.

Cardiac Stress Tests — Picking the Correct Test

To determine the correct stress test, go through the following scenarios. These are diagramed as a flowchart in Figure 5-1, Stress Testing Algorithm.

An **exercise stress test** (ETT, stress echo, MPI) is always preferred if the patient has no limitations to exercise. If the resting ECG is normal, proceed with exercise treadmill test (ETT)—no imaging is needed. If the resting ECG is abnormal, perform exercise testing with myocardial perfusion imaging (MPI).

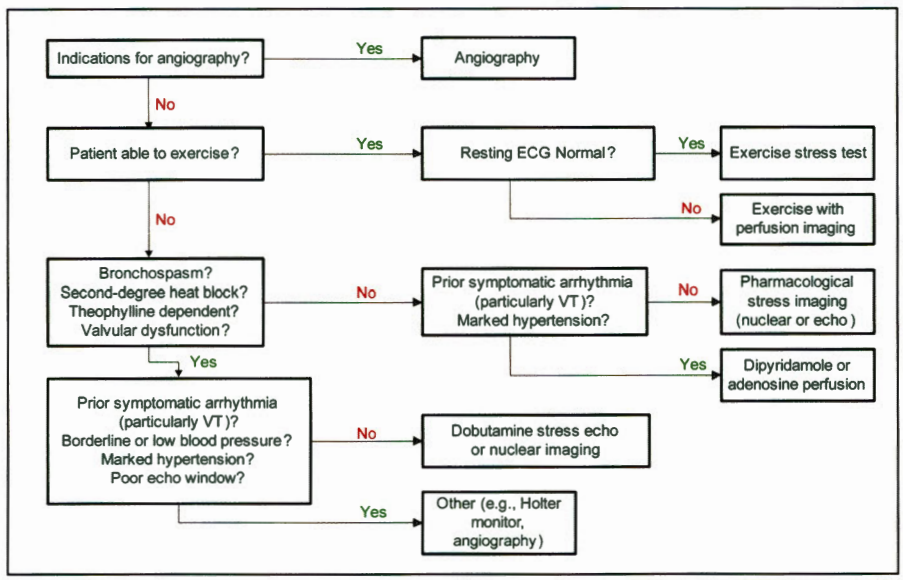


Figure 5-1: Stress Testing Algorithm

Pharmacologic stress test is done if the patient cannot do more than moderate exercise or is unable to increase the heart rate (e.g., pacemaker).

Follow these indications when choosing the proper agent:

- If the patient simply is unable to walk and has no other issues, use any of the agents: vasodilators for MPI or dobutamine for stress echo.
- If the patient has bronchospasm or severe carotid artery stenosis, use dobutamine.

Quick Quiz

- When is PCWP increased?
- When is diastolic pressure equal in all 4 chambers?

- If the patient has prior ventricular tachycardia (VT) or severe hypertension (HTN), use a vasodilator (adenosine, dipyridamole, or regadenoson), not dobutamine.
- Again, if the patient has a LBBB or paced ventricular rhythm, use a vasodilator with MPI, not dobutamine.

One more time: Do not use adenosine or dipyridamole in someone with asthma (regadenoson still being evaluated) and do not use dobutamine in someone with a history of VT, uncontrolled HTN, or a paced ventricular rhythm.

CARDIAC SCANS / CATHS

Contrast Cardiac Catheterization

All contraindications to cardiac catheterization are relative. Ventriculograms and aortic root angiography can be done at the same time as the coronary angiogram.

Coronary angiography is the gold standard for the diagnosis of coronary artery disease (CAD) and carries ~ 1% complication rate. It is also used to assess for other coronary processes (e.g., congenital anomalies, spasms, aneurysms, and myocardial bridge).

Contrast ventriculography is used for determining ejection fraction, wall motion abnormalities, ventricular dilatation, degree of mitral regurgitation, and the presence of a ventricular aneurysm.

These studies all involve arterial access, radiation exposure, and contrast exposure.

Cardiac CT

Cardiac CT is a newer, noninvasive modality for imaging the heart. Cardiac CT includes:

- Coronary CT angiography (CTA)
- Coronary artery calcium (CAC) scoring
- Assessment of ventricular structure and systolic function

CTA requires IV contrast; also, the heart rate must be < 60 bpm and regular, and patients must be able to hold their breath. The negative predictive value of CTA is very high; that is, a negative CTA is very helpful in excluding significant coronary artery disease. The specificity of both calcium scoring and CTA decline with increasing age, making these tests better suited for younger individuals.

Coronary artery calcium (CAC) scanning detects atherosclerosis and, unlike CTA, does not require IV contrast. Current applications for CAC screening are evolving; it is currently used for further risk stratification of intermediate-risk patients (e.g., diabetics) and for ruling out obstructive disease in the symptomatic patient with low probability of disease.

A noncontrasted chest CT (which differs from a dedicated cardiac CT) is highly effective in assessing for pericardial thickening if constriction is a concern.

Cardiac MRI

Static and dynamic cardiac MRI (CMRI) allows high-resolution imaging of ventricular function, valvular motion, and myocardial perfusion.

CMRI is useful to assess cardiac structure and function, valve motion, valvular regurgitation, coronary takeoff, the great vessels, pericardial disease, myocarditis, and infiltrative diseases.

CMRI can also be used to assess for myocardial ischemia and post-MI tissue viability.

PULMONARY ARTERY CATHETERIZATION

Pulmonary artery catheterization (PAC) can be used to assess right and left filling pressures, cardiac output, RV and PA pressures, and systemic and pulmonary vascular resistance. This is useful to determine a patient's volume status, causes of shock, and existence of pericardial disease.

The pulmonary capillary wedge pressure (PCWP) is the dampened LA pressure that reflects left ventricular end-diastolic pressure (LVEDP) in most cases. This reflects LVED volume. [Know this entire topic!]

Normal pressures (mmHg):

- RA < 7, RV = 30/7. Jugular venous distension in the upright patient indicates an elevated RA pressure > 7 cm H_2O (5 mmHg).
- PCWP < 12. PCWP increases with LV systolic and diastolic failure, mitral stenosis, aortic and mitral insufficiency, tamponade, and constrictive pericarditis. Consider LV failure if the PCWP is > 15–18; PCWP 15–25 causes dyspnea on exertion (DOE); and PCWP 25–35 causes dyspnea at rest, orthopnea, and interstitial edema. Pressure > 35 (acutely) causes frank pulmonary edema.

Note: The RA pressure and PCWP also increase with decreased compliance of the ventricle (as in LVH and RVH).

A few PAC scenarios are shown in Table 5-1.

1) Normal: Notice in the examples that the diastolic PA pressure is usually very close to PCWP (usual difference < 5) except in #6, in which there is pulmonary hypertension!
2) Diastolic pressure in all 4 chambers is equalized in both pericardial tamponade and constrictive pericarditis. See Pericardial Diseases discussion for the tests that differentiate between these disorders (page 5-49).

Table 5-1: Pulmonary Artery Catheterization Scenarios

	RA Press	PA Press	PCWP	BP
1 (normal)	0–5	(13–28)/(3–13)	3–11	110/70
2	18	32/18	19	70/50
3	15	21/11	10	70/50
4	18	30/20	20	70/50
5	18	90/32	30	110/70
6	18	90/32	10	110/70

3) If the cardiac output and PCWP are decreased and the RA pressure is elevated in the setting of an acute inferior MI, the cause is RV infarction with secondary right-sided failure. The RV has decompensated and is unable to fill the left side of the heart. Treatment is to give fluid until the blood pressure returns to normal. This sounds like stressing an already stressed RV—and it is—but there is a net positive effect when BP and, hence, coronary artery blood flow are returned to normal and heart rate is reduced. Think of this in a hypotensive patient with an inferior infarction and raised JVP.
4) If the cardiac output is low, PCWP high, and RA pressure high, the patient has biventricular failure with cardiogenic shock. Treatment is to give diuretics, preload and afterload reducers, and inotropes. In a typical case, a patient gets nitroprusside, nitroglycerin, milrinone, or dobutamine.
5) Mitral stenosis (or LV failure) with 2° RV failure.
6) Pulmonary hypertension.

Also know that septic shock is mainly due to a low systemic vascular resistance. These patients will have low BP, SVR, and PCWP—and a high CO.

CARDIAC BIOPSY

Endomyocardial biopsy is used to evaluate the cause of a cardiomyopathy or myocarditis in patients where the diagnosis is uncertain and would change management, or if the patient is not responding to therapy. Monitoring cardiac transplant rejection and anthracycline cardiotoxicity are the 2 major indications for endomyocardial biopsy. Other indications include diagnosis for secondary causes of cardiomyopathy, myocarditis (when there is a history of congestive heart failure in the preceding 6 months), and differentiation between restrictive and constrictive cardiomyopathies.

The sensitivity of endomyocardial biopsy in many conditions that affect the heart focally is relatively low, so a "negative" biopsy is not as helpful as a "positive" one.

Alcoholic cardiomyopathy cannot be diagnosed by biopsy; it is diagnosed by history and exclusion of other causes.

PHYSICAL EXAM

Note

Know this physical exam topic perfectly! You should know normal findings as well!

Pulses

- Pulsus paradoxus (decreased pulse amplitude with inspiration seen as absence of Korotkoff sounds during inspiration) is present with:
  - cardiac tamponade (especially),
  - constrictive pericarditis,
  - asthma, and
  - tension pneumothorax.
- The paradox is that, when severe, you may hear a heartbeat but not feel a pulse during inspiration. This can be observed clinically by auscultating the BP and listening for an exaggeration of the normal inspiratory decrease in systolic BP (> 10 mmHg). Note: Korotkoff sounds are those heard during blood pressure determination with a cuff.
- Pulsus bisferiens (bifid with 2 systolic peaks per cardiac cycle) is seen with aortic regurgitation (with or without stenosis!) and hypertrophic cardiomyopathy (HCM, page 5-42).
- Pulsus alternans (varying pulse pressure with a regular pulse rate) is seen with severely depressed systolic function of any cause that leads to decreased stroke volume.
- Pulsus parvus et tardus (low amplitude, slow upswing) = aortic stenosis.
- Brachiofemoral delay, the femoral pulse occurring after the brachial pulse, is present in coarctation of the aorta.
- Pulse asymmetry occurs in aortic dissection, with good upper-extremity pulses and diminished or absent lower-extremity pulses, or the asymmetry occurs between the left and right extremities.
- Peripheral arterial disease (PAD; previously called peripheral vascular disease, PVD) may cause decreased or absent peripheral pulses; a bruit may be heard over the more proximal artery (such as the femoral artery) as well.

Heart Sounds and Murmurs

Heart sounds and murmurs. [Again, know this topic! Know the heart sounds tables in the Valve Disorders discussion (Table 5-8 and Table 5-9 on page 5-30 and page 5-31) perfectly!] Learn these topics so you can determine how one abnormal finding on, say, a heart sound suggests certain findings on ECG and chest x-ray.

QuickQuiz

- What is pulsus bisferiens? What does it indicate?
- What does pulsus alternans indicate?
- With what condition do you see pulsus tardus?
- When is a persistently split S_2 heard?
- What causes a paradoxically split S_2?
- When is an S_3 important?

Murmurs

All valve murmurs increase in intensity when blood flow increases across the valve. Standing and the strain phase of Valsalva decrease right and left cardiac filling and cause the sound of most murmurs to decrease, but these actions increase the intensity of the murmurs of mitral valve prolapse (MVP) and hypertrophic cardiomyopathy (HCM; formerly IHSS). Squatting and lying down (or passive straight-leg raises if already supine) increase cardiac volume. This increased volume also increases intensity of all murmurs except, again, MVP and HCM.

Sustained handgrip (20–30 seconds) boosts systemic vascular resistance and left ventricular volume and therefore decreases the murmurs of HCM and aortic stenosis (AS). It prolongs the murmur of MVP due to earlier prolapse of the valve; thus, it helps differentiate between these. Typically, you will use handgrip to differentiate between AS (murmur decreases) and MVP (murmur increases in duration).

Right-sided murmurs and heart sounds are louder during Inspiration and any maneuvers that increase venous return such as passive leg raising and abdominal compression. Left-sided murmurs and heart sounds are louder during Expiration. The only semi-exception to this rule is a right-sided ejection click due to pulmonic stenosis; this disappears with inspiration. (On a chest x-ray, pulmonic stenosis may show as an enlarged pulmonary artery.)

Heart Sounds

S_1 is caused by the closing of the mitral and tricuspid valves. S_1 intensity is decreased when there is a prolonged PR interval, mitral regurgitation, acute aortic regurgitation (increased LV pressures cause early valve closure), or with a severely calcified mitral valve. S_1 intensity is increased (i.e., the mitral valve slams shut) by a short PR interval, mitral stenosis, or hyperdynamic ventricular function.

S_2 is the closing of the aortic (A_2) and pulmonic (P_2) valves at the end of systole. P_2 usually occurs just after A_2; this physiologic split is increased with inspiration, because the increased volume of blood in the right ventricle prolongs RV systole and delays closure of the pulmonic valve. It usually disappears on expiration.

A persistently (or widely) split S_2 can vary with respiration but does not disappear on expiration. A widely split S_2 that varies with inspiration (but never completely disappears) may be due to pulmonic stenosis, acute pulmonary embolism, ectopic or pacemaker beats originating in the left ventricle, or right bundle-branch block (RBBB)—all of which cause delayed or prolonged contraction of the right ventricle. A widely split S_2 may also be caused by early closure of the aortic valve, as in mitral regurgitation. Pulmonic stenosis is especially likely if the patient has an ejection click that disappears with inspiration.

You hear a fixed split S_2 when there is an atrial septal defect. The patient presents with a fixed, split-second heart sound, a systolic ejection murmur (SEM), and has pulmonary vascular congestion on the chest x-ray. You can also hear a fixed split S_2 with RV failure when the stroke volume is unable to increase with inspiration.

A delay of aortic closure (A_2) causes a paradoxically split S_2, with P_2 occurring before A_2. This delay is usually caused by LBBB and ectopic or pacemaker beats originating in the right ventricle. Advanced HCM is another cause.

S_3 just follows S_2 and indicates the end of rapid ventricular filling; this is the first part of diastole, when the first 70% of ventricular filling occurs as the ventricle relaxes. The sound is thought to be due to the tensing of the chordae tendineae. You often hear it in normal children and in persons with high cardiac output, such as pregnant women, but it is usually an abnormal finding in patients > 40 years of age. In these patients, it can be from any condition that increases early LV filling rate or volume, such as acute ventricular decompensation or severe aortic or mitral regurgitation. S_3 in a patient with known left ventricular dysfunction is a poor prognostic indicator—in general, as well as for surgery. Both S_3 and S_4 are best heard in left lateral decubitus position using the bell.

S_4 is heard just before S_1 at the end of diastole. The S_4 sound is caused by ventricular filling during atrial contraction, and you hear it in patients with decreased ventricular compliance. Increased stiffness of the ventricles causes forceful atrial contraction and causes S_4. You may hear S_4 in ischemic heart disease, aortic stenosis, hypertrophic cardiomyopathy, diabetic cardiomyopathy, and hypertensive heart disease with concentric hypertrophy. You will not hear an S_4 during atrial fibrillation because the sound requires atrial contraction. S_4 is also not audible in mitral stenosis, where there is obstruction of the ventricular inflow.

Venous Waveforms

Venous waveforms: Jugular venous pressure and waveforms are typically examined on the right side of the neck. [Know these!] See Table 5-2. Also see Table 5-8 on page 5-30 for a review of the valve disorders.

- Large, right-sided *v* waves are seen in ventricular septal rupture and tricuspid regurgitation.
- With severe mitral regurgitation, there are tall, left-sided *v* waves from the regurgitation during systole. These are not seen on the JVP but on Swan-Ganz monitoring.
- Rapid *x* and *y* descents are seen with constrictive pericarditis, whereas only a rapid *x* descent is seen in tamponade (loss of the *y* descent).
- Large, right-sided *a* waves are seen in tricuspid stenosis (TS), severe pulmonic stenosis, and severe noncompliant RVH.
- Large, left-sided *a* waves are seen with mitral stenosis (MS). "Cannon" *a* waves occur in complete heart block, ventricular tachycardia, or asynchronous ventricular pacing and all conditions with AV dissociation (times when the atrium is contracting against a closed tricuspid valve).
- Slow *y* descent is from delayed atrial emptying as in tricuspid stenosis.

HYPERTENSION

Suspect secondary causes of hypertension (HTN) in patients who develop HTN at a young age, who have drug-resistant HTN, or who develop uncontrolled HTN that was previously well controlled.

Systolic abdominal bruits (without a diastolic bruit) suggest renal vascular hypertension. Bilateral renal artery stenosis can lead to severe exacerbation of hypertension and decline in renal function with initiation of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs). Renal artery stenosis can be diagnosed by renal artery Doppler assessment, selective renal angiography, CT angiogram (CTA), or MRA.

Think of primary hyperaldosteronism in a hypertensive patient with hypokalemia and low renin.

Think of pheochromocytoma in a hypertensive with recurrent and intermittent episodes of severe hypertension, frequently accompanied by palpitations and severe apprehension.

Much more on hypertension in the Nephrology section, Book 2.

CARDIAC MEDICATIONS

Refer to Table 5-3 for an overview and comparison of commonly used cardiac medications. Pay attention to those that prolong survival!

CARDIAC ISCHEMIA

OVERVIEW

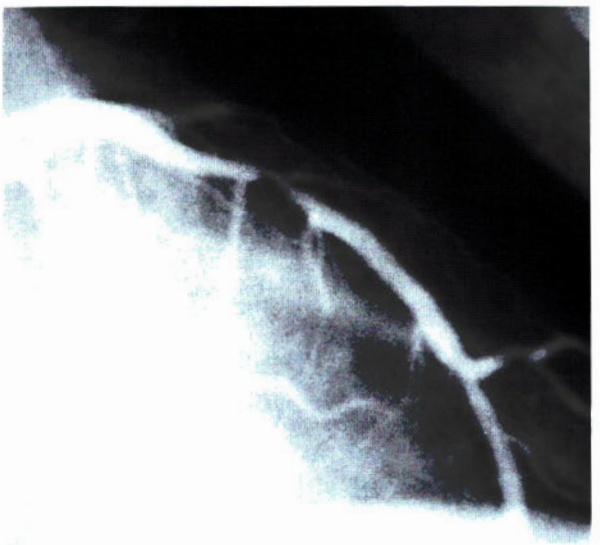
Angina is chest pain caused by a "supply-demand" mismatch between coronary perfusion and cardiac workload. It is typically classified as either stable or unstable (new onset or increased frequency). Atherosclerotic coronary artery lesions are the most common source of a supply problem (Image 5-4). Plaque rupture (from ulcerated plaques) is the most common underlying process triggering acute coronary syndromes. These plaques provide a nidus for platelet aggregation.

Table 5-2: Venous Waveforms in a Clinical Setting

Condition	Neck Vein Appearance	Other Diagnostic Features
Pulmonary HTN	Elevated *a* and *v* waves	Other physical exam findings of pulmonary HTN
Tricuspid regurgitation	Large *v* waves	TR murmur, pulsatile liver
Constrictive pericarditis	Rapid *x* and *y* descents	Kussmaul sign, pericardial knock
Tamponade	Rapid *x* descent	Pulsus paradoxus, hypotension
Tricuspid stenosis	Slow *y* descent	TS murmur
Restrictive cardiomyopathy	Rapid *x* and *y* descents	Low-voltage ECG, echo, myocardial biopsy
Tension pneumothorax	Distended neck veins	Dyspnea, unilateral absent breath sounds, deviated trachea, chest x-ray
Superior vena cava syndrome	Unilateral distended neck veins	Facial edema and cyanosis, diagnosis of cancer
AV dissociation	Irregular cannon *a* waves	ECG
RV infarction	Elevated *a* and *v* wave	Acute inferior MI, Kussmaul sign
ASD	Large *v* waves and rapid *y* descent	Fixed split S_2, echo

Quick Quiz

- When are large *v* waves seen on the left side? Right side?
- When is rapid *x* and *y* descent seen?
- When are large, right-sided *a* waves seen?
- When are large, left-sided *a* waves seen?
- When are "cannon" *a* waves seen?
- When does a slow *y* descent occur?
- True or false? A systolic abdominal bruit without a diastolic bruit suggests renal vascular hypertension.



Hank Morgan/Photo Researchers, Inc.

Image 5-4: Angiogram showing narrowing in coronary artery.

There are many causes of increased demand (e.g., tachycardia, fever, and thyrotoxicosis) and many other causes of a decreased supply (e.g., hypotension, coronary vasospasm, anemia, and hypoxia). Coronary blood flow is impaired in conditions such as severe aortic valve disease with left ventricular hypertrophy (LVH), hypertension, idiopathic dilated cardiomyopathy, and hypertrophic cardiomyopathy, even in the absence of epicardial CAD.

Table 5-3: Common Cardiac Medications

Medication	Negative Inotrope	Negative Chrono-trope	Negative Dromo-trope	Vaso-dilator	Anti-anginal	Prolong Survival Post-MI	Prolong Survival in HF	Indications
Digoxin	N	+	+	N	N	N	N	Systolic HF, arrhythmias
Beta-blockers	+++	+++	+++	N	Y	Y	Y	HTN, angina, HF, arrhyth-mias
Carvedilol	++	+++	+++	Y	Y	Y	Y	HTN, angina, HF, arrhyth-mias
Nifedipine	++	N	N	Y	Y	N	N	HTN, angina
Amlodipine	+	N	N	Y	Y	N	Y (in DCM)	HTN, angina, DCM
Diltiazem	++	++	++	Y	Y	N	N	HTN, angina, arrhythmias
Verapamil	+++	+++	+++	Y	Y	N	N	HTN, angina, arrhythmias
Nitrates	N	N	N	Y	Y	N	Y (with hydralazine)	Angina, HF
ACEIs	N	N	N	Y	N	Y	Y	HTN, HF
ARBs	N	N	N	Y	N	Y	Y	HTN, HF
Hydralazine	N	N	N	Y	N	N	Y (with nitrates)	HTN, HF
Spironolac-tone	N	N	N	N	N	N	Y	HTN, HF
Eplerenone	N	N	N	N	N	Y (w/HF)	Y (p MI)	HF post MI

Note: Only ~ 20% of patients actually have classic angina at the moment of ischemic ST changes. Silent myocardial ischemia is painless but just as harmful as angina-associated ischemia. Silent ischemia is seen frequently in diabetic patients as well as those with prior ischemic events. The "silent" ST depression seen in these patients on stress test is associated with decreased perfusion. Silent ischemia, myocardial infarctions, and thrombotic strokes tend to occur in a circadian pattern, with the highest incidence in the early morning hours.

The distinction between stable and unstable angina is a key factor in determining management/diagnostic strategies.

Unstable angina may be due to an ulcerated or ruptured plaque and falls within the spectrum of acute coronary syndromes; this warrants immediate/emergent medical attention and usually inpatient monitoring. (See Acute Coronary Syndrome on page 5-12.)

Stable angina, however, can frequently be evaluated in the outpatient setting and may not require revascularization to improve patient outcomes.

The most important, easily determinable prognostic factor in patients with coronary artery disease is the degree of LV dysfunction. (If severe, it may be a reflection of multi-vessel or left main/left main-equivalent disease.)

The exercise treadmill test is an excellent, objective way to determine the severity of angina and to determine prognosis. Patients who are able to go to stage 4 of Bruce protocol (Table 5-4) have nearly 100% 5-year survival, while those who cannot get past stage 1 have only a 50% 5-year survival! Note that coronary angiography is not required for the determination of either of these prognostic factors!

Spasms of the coronary arteries usually show up as transient ST-segment elevation if they occur during stress testing.

What causes resting ST-segment elevation? Acute MI, pericarditis, LV aneurysm, LBBB, ventricular pacing, LVH, and benign early repolarization.

Hibernating myocardium is chronically underperfused myocardium. There is no irreversible myocyte injury.

Table 5-4: Bruce Protocol

Stage	Min	% Grade	MPH	METs
1	3	10	1.7	4.7
2	6	12	2.5	7.0
3	9	14	3.4	10.1
4	12	16	4.2	12.9
5	15	18	5.0	15.0

When perfusion is restored to normal, contractility should return to normal.

Reperfusion injury occurs when a severely ischemic myocardium is reperfused after ~ 1 hour, causing further irreversible microvascular damage and damage to the myocardial cells.

Stunned myocardium is also the result of acute ischemia. From the time perfusion is restored, it may take 7–10 days for the ventricular function to return to normal.

Treatment of all angina: Modify risk factors and correct aggravating factors such as anemia, hypertension, smoking, drug abuse, and noncompliance. (Good luck!)

Beta-blockers and nitrates are the staples of medical treatment, but calcium channel blockers may also help. Nifedipine and amlodipine decrease angina by both coronary artery vasodilation and peripheral vasodilation (decreases workload). The main anti-anginal effect of diltiazem and verapamil is due to their negative chronotropic effect.

ASA decreases mortality and MI occurrence in unstable (and probably stable) angina. Clopidogrel (Plavix®) may be used in patients who cannot tolerate or are allergic to ASA or who have an indication to take this in addition to ASA.

Ranolazine (Ranexa®) may also have a role in some patients with persistent angina on maximal standard therapy. It is thought to work by inhibiting the late sodium current in cardiac myocytes, thereby reducing sodium and calcium overload that follows ischemia. This improves myocardial relaxation and reduces left ventricular diastolic stiffness, which in turn enhances myocardial contractility and perfusion.

More on anti-anginal drugs:

- Nitrates, beta-blockers, and calcium channel blockers all decrease myocardial O_2 demand, and all decrease afterload.
- Nitrates decrease preload more than afterload and also dilate coronary vessels. Acute preload reduction is why nitrates can cause severe decompensation in patients with an acute right ventricular MI. Patients on nitrates get a sympathetic reflex increase in heart rate (HR). Nitrates are degraded in the liver. Tolerance develops rapidly with nitrates (tachyphylaxis), but you can avoid tolerance by having a 6-hour "nitrate-free window" once a day; i.e., between midnight and 6 a.m. Development of tolerance is less likely with mononitrates than with dinitrates.
- Beta-blockers decrease myocardial O_2 demand by decreasing HR, blood pressure (BP), and contractility. Beta-blockers complement nitrates well because they decrease the reflex tachycardia.
- Calcium antagonists: The combined vasodilatory and antihypertensive effects make them ideal for patients with angina/ischemia and hypertension.

QuickQuiz

- What time of day does the highest incidence of spontaneous ischemic cardiac events occur?
- What is the most important prognostic factor in a patient with CAD?
- What does ST-segment elevation suggest on an exercise ECG stress test?
- What are causes of resting ST-segment elevation?
- What are the main drugs used to treat angina?
- Why should you determine the probability of CAD in a person with intermittent chest pain?
- For what groups of patients do you determine ejection fraction as part of the workup for chronic stable angina?

See Table 5-3. Verapamil and diltiazem should be used cautiously in patients with systolic heart failure due to the negative inotropic effects. Short-acting nifedipine is contraindicated due to steep drops in BP and reflex tachycardia.

- There is a high probability of coronary thrombus formation with unstable angina, so always use either IV heparin or subcutaneous low-molecular-weight heparin (LMWH) if there are no contraindications.

The following are now recommended concomitantly with heparin and for follow-up medical therapy for unstable angina:

- Aspirin daily for life
- Clopidogrel x 1 month and ideally up to a year (particularly if a stent is placed)

EVALUATION OF CHRONIC STABLE ANGINA

Note

The following is drawn from the 2007 ACC/AHA guidelines.

Evaluation is basically a 3-step process:

1) Determine the probability of coronary artery disease (CAD).
2) Determine the relative risk.
3) Determine if the patient needs further workup.

1. History and Physical Exam: Determine Probability of CAD

First estimate presence and severity of CAD (based on factors below). This step is very important because it determines pretest probability for the rest of the tests, which improves the positive and negative predictive values of these tests.

After other causes of chest pain are ruled out, determine the following:

- Typical vs. atypical chest pain is determined by assessing quality, location, and duration of the chest pain. Also, what precipitates or relieves the pain?
- Cardiovascular risk factors: especially DM, HTN, smoking, hyperlipidemia, family history of CAD, and postmenopausal status in women. History of substance abuse must be obtained. Cocaine can accelerate atherosclerosis, enhance platelet aggregation, cause vasospasm, and increase myocardial oxygen demand.
- Comorbid conditions that:
  - increase cardiac load (hyperthyroidism, cocaine use, severe uncontrolled HTN, significant valvular disorder), or
  - decrease cardiac blood supply (anemia, hypoxemia, and increased blood viscosity).

From the above, determine if the patient has high, intermediate, or low probability of CAD. Low probability needs no further testing. Those with intermediate or high probability of CAD should undergo "risk stratification" with further testing (discussed next).

2. Noninvasive Tests for Chronic Stable Angina: Risk Stratification

ECG: especially for checking ST-T wave changes that suggest ischemia, Q waves, and LVH. Other findings (e.g., RBBB, LBBB, atrial fibrillation, bifascicular block) are not specific indicators of CAD.

Chest x-ray is done only if there are signs of heart failure (HF), valvular disorders, or pericardial disease.

Ejection fraction determination (echocardiogram, myocardial perfusion imaging, or invasive left ventriculography) is done only on patients with a history of MI, Q waves on ECG, or symptoms of heart failure.

Exercise testing is the most important test in risk stratification. For those who can exercise, do exercise testing for all with stable angina, but add imaging for those who have:

- > 1 mm resting ST depression
- Other significant ECG changes (that are not LBBB or paced rhythm) such as LVH
- WPW
- On digoxin

If the patient is unable to exercise, has no LBBB, no paced ventricular rhythm:

- do vasodilatory (adenosine, regadenoson, dipyridamole) myocardial perfusion imaging (MPI), or
- do dobutamine echo. (See prior section on stress testing on page 5-2.)

If the patient has LBBB or paced ventricular rhythm:

- do vasodilatory myocardial perfusion imaging instead of exercise, but
- do not use dobutamine for paced rhythm (okay for LBBB).

Skipping the stress testing is indicated only for those with severe comorbid conditions that preclude any further cardiac stress or possibility of revascularization. (In this case, the test results won't change your management strategy, so don't order it.)

More recently, coronary computed tomographic (CT) angiography has been used to assess epicardial coronary artery anatomy and coronary calcification. Criteria for its application have not been finalized. Routine use of this technology in those with stable CAD is not recommended.

3. Determination of Further Workup in Chronic Stable Angina

From the above, determine the probability of death or MI (high, intermediate, or low):

- If high (i.e., large or severe ischemic burden on imaging, low ejection fraction, poor exercise capacity with typical symptoms or ECG changes), or if intermediate and you still need more information, do angiography.
- If low (i.e., small, limited area of ischemia with good exercise capacity; or a fully negative stress test), discuss with the patient options for evaluation, risk-factor modification, and treatment.
- Patients with chronic, stable angina can safely be managed with an initial conservative strategy directed toward medical control of risk-factor modification and symptom relief (discussed next).

TREATMENT OF CHRONIC STABLE ANGINA

Focus treatment on risk-factor modification and symptom control.

The ACC/AHA 2007 guidelines added the following recommendations:

- Keep BP < 140/90 or < 130/80 with DM or kidney disease; use beta-blockers and/or ACEI first.
- ACEI in all patients if possible (no matter what BP is).
- Daily physical activity
  - 30–60 min/day for 7 days/week, and
  - weight-lifting for 2 days/week.
- Men waist < 37–40"; women < 35".
- Encourage omega-3 fatty-acid intake (dietary or supplemental).
- LDL < 100 for all—and < 70 for most—on high-dose statin; add niacin after statin if non-HDL-C is still too high.
- Influenza vaccine yearly.

CARDIOVASCULAR DISEASE PREVENTION IN WOMEN

A 2011 update of the AHA Guidelines for the Prevention of CVD in women warns that:

- Hormone therapy should not be used as primary or secondary prevention.
- Antioxidants (i.e., vitamin C, E, beta-carotene) should not be used as primary or secondary prevention.
- Folic acid should not be used.
- Do not use aspirin in healthy women < 65 years of age for primary prevention of MI. (Aspirin is okay for those ≥ 65.)

ACUTE CORONARY SYNDROME

CLASSIFICATION OF ACS

This is another area from which many Board questions are drawn. [Know this well!]

Acute coronary syndromes (ACSs) result in acute ischemia, usually caused by atherosclerotic plaque rupture, fissuring, erosion, or a combination with superimposed intracoronary thrombosis and are associated with an increased risk of cardiac death and myonecrosis. Acute coronary syndromes are divided into 2 types:

1) Non-ST elevation events
2) ST elevation events

Non-ST elevation events are either unstable angina (UA) or non-ST elevation MIs (NSTEMIs). You will see these combined as UA/NSTEMI.

ST elevation events are ST elevation MIs (STEMIs). STEMI occurs when a coronary artery thrombus develops rapidly at a site of vascular injury from such causes as cigarette smoking, hypertension, and lipid accumulation. When the surface of a plaque becomes disrupted, conditions (local or systemic) favor thrombogenesis. Rarely, STEMI may be due to occlusion by coronary emboli, congenital abnormalities, coronary spasm, and a wide variety of systemic inflammatory diseases.

The term "Q wave MI" was once considered synonymous with "transmural" infarction. STEMIs are more likely to be Q wave infarctions, and NSTEMIs are more likely to be non-Q wave infarctions; however, neither Q wave nor non-Q wave ECG changes precisely define the depth of the infarcted area. For all practical purposes, the terms "Q wave" and "non-Q wave MI" are no longer used, and MI events are now categorized as either being a STEMI or NSTEMI.

Patients with NSTEMIs have a smaller size of infarcted area and decreased early mortality but a higher risk for persistent angina, reinfarction, and death within several months!

Quick Quiz

- A patient undergoing a workup for chronic stable angina is unable to exercise and has a LBBB. What types of stress tests are recommended and not recommended?
- For what patients do you not do stress and exercise testing as part of the workup for chronic stable angina?
- A patient undergoing a workup for chronic stable angina is determined to be at high risk for death. What is the next step?
- How are troponin I and T used? How long do they stay elevated after an MI?

So, although NSTEMIs have a lower initial mortality, they have a higher 6-month mortality compared to STEMIs. Also, know that patients with NSTEMIs are more likely than those with STEMIs to have had a prior MI or angina!

Differential diagnosis of prolonged chest pain includes: ACS (MI), aortic dissection, pericarditis, esophageal or biliary tract problems, pneumothorax, pulmonary embolism, pleuritic pain related to pneumonia, musculoskeletal inflammation, and psychogenic causes.

NOTES

15% of acute myocardial infarctions (AMIs) are asymptomatic.

MI without chest pain or with atypical chest pain is more common in the following:

- Elderly (about 2/3 of these patients > 75 years of age)
- Diabetics
- Women
- Those with prior CAD

Mitral regurgitation due to papillary muscle dysfunction is seen more commonly with inferior MIs.

Ventricular septal defect (VSD) from septal rupture is seen more commonly with anterior and inferior MIs.

Arrhythmias in the first 48 hours after MIs are due to acute ischemia and do not imply a need for long-term antiarrhythmic therapy.

Inferior vs. anterior MI: Inferior MIs are associated with more stable arrhythmias, such as junctional escape and Mobitz I, instead of the poorer prognosis with Mobitz II and BBBs, which are more often seen in anterior MIs. Even when Mobitz II or complete heart block is seen in an inferior MI, it is usually temporary. Also, the amount of infarcted myocardium is usually larger with anterior MIs. Unfortunately, septal rupture can occur in either type. (See Complications on page 5-20.)

MARKERS FOR AMI

Serum markers that increase in response to acute myocardial necrosis include troponins, creatine kinase MBs (CKMBs) and myoglobin (Table 5-5).

[Know all of the following!]

Assays to detect components of cardiac muscle, **troponin I** and **troponin T** (cTnI and cTnT), are now the gold standard for the detection of myocardial necrosis. The level of either of these has also been shown to have prognostic implications in the setting of an acute MI. The 2 troponin assays are equally useful, and local preferences dictate which one is used.

Troponins first become elevated at 3–12 hours following an MI and peak at about 24 hours after the event. They may remain elevated for a week or more after an MI, which can muddy the picture in those suspected of having a recurrent MI—use myoglobin and/or CKMB instead (see below). On the other hand, because they do stay elevated so long, troponins are beneficial in the workup of those who present more than 24–48 hours after onset of symptoms.

Be aware that troponins can also be elevated in chronic renal failure, myopericarditis, congestive heart failure (CHF), sepsis, pulmonary embolism, and cardiac trauma. Although troponins are sensitive markers for AMI, they are not highly specific; therefore, they are good for excluding AMI but not as good for confirming one. Sensitive but not specific.

CK and its isozyme **CKMB** have been the traditional markers of choice for myocardial necrosis. CK is a nonspecific marker of muscle injury (both skeletal and myocardial), while CKMB is specific to myocardium. Like the troponins, these become detectable at 3–12 hours following an MI event and peak at 24 hours. CKMB typically returns to normal range after 48–72 hours, earlier than the troponins.

Both CK and CKMB can be elevated due to non-MI causes, such as in rhabdomyolysis. The CKMB:total CK ratio can be useful to distinguish between cardiac and noncardiac sources of CK elevation—although this is not fully reliable in very severe cases of muscle injury.

Table 5-5: Acute Myocardial Infarction Markers

Marker	Initial Elevation	Peak Elevation	Return to Normal
Myoglobin	1–4 hr	6–7 hr	24 hr
Troponin I	3–12 hr	24 hr	7–10 d
CKMB	3–12 hr	24 hr	2–3 d
CKMB isoform	2–6 hr	18 hr	2 d

Myoglobin is a very sensitive, but nonspecific, test for acute myocardial necrosis. It rises very rapidly, so a negative myoglobin in the first few hours is useful in ruling out an infarction (high negative predictive value). Because it is excreted quickly in the urine, myoglobin is also the quickest to return to normal—within 24 hours—so it can be potentially useful to help evaluate recurrent chest pain soon after an MI, when troponins and CKMB are still elevated. Because of its low specificity, it is not frequently used in clinical practice.

The most sensitive and specific markers now used are a combination of troponin I or T and CKMB.

With both the troponins and CKs, the overall trend is important and gives added information beyond a single elevated value ("trending enzymes"). An individual whose enzymes continue to rise is a very different patient from someone whose enzymes peaked earlier in the day, even in the absence of symptoms!

TREATMENT OF ACS

Overview

In general, the sequence to address acute coronary syndrome is to first take proper care of the patient prior to arrival in the emergency department (ED). Once the patient arrives, you do an assessment, draw labs, and do an ECG. Based on these results, you determine if the patient with suggestive symptoms is actually having ACS.

Figure 5-2 diagrams this process of determining if the patient has ACS.

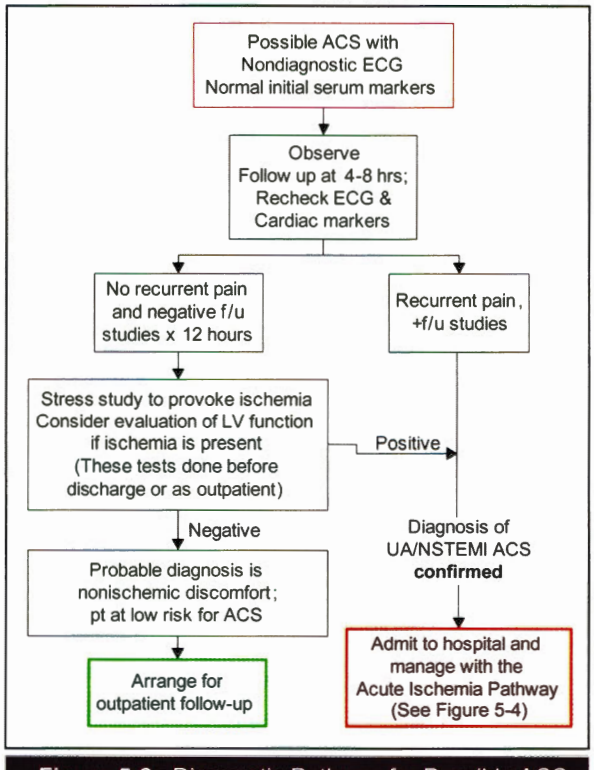


Figure 5-2: Diagnostic Pathway for Possible ACS

Figure 5-3 diagrams the process of managing UA/NSTEMI ACS vs. ST-elevated ACS.

If the patient has definite ACS, follow one of the following protocols:

- Acute Ischemia Treatment Pathway (for UA/NSTEMI Figure 5-4)
- Management of ACS with STEMI or new LBBB (Figure 5-5 on page 5-18)

Now, let's go through these steps in more depth.

Pre-ED Arrival (In the Field) Guidelines

2007 ACC/AHA guidelines recommend the following:

- Call 911; do not allow the patient to be brought in by relatives.
- Give nonenteric coated ASA (162–325 mg) as bite and chew x 1.
- Nitroglycerin: If the patient has it, give only 1, then:
  - Unimproved or worsening—give no more; call 911.
  - Improved—can repeat to max of 3.
  - Note: If the patient has taken a phosphodiesterase inhibitor (e.g., sildenafil or vardenafil) within 24 hours, do not give nitroglycerin due to the risk of severe hypotension!
- ECG in the field by EMS.
- Be prepared to recognize and manage ventricular arrhythmias.

Evaluation of Patients with Symptoms Suggestive of ACS

Early risk stratification: For patients who present to the ED with symptoms suggestive of ACS, immediately (within 10 minutes) get an ECG, draw blood for cardiac markers, give aspirin if not contraindicated, and conduct a directed history and physical examination.

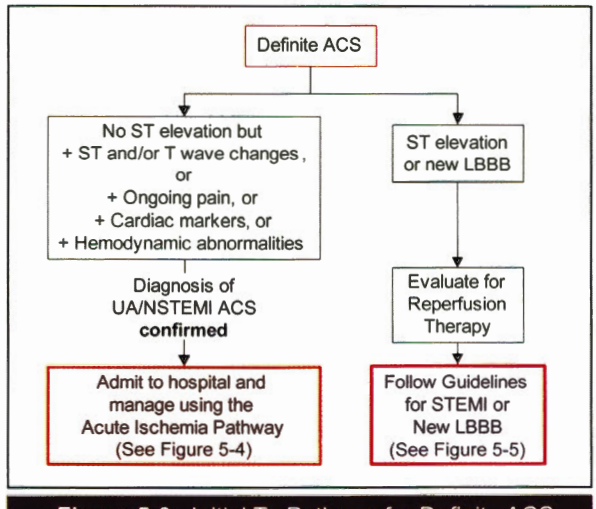


Figure 5-3: Initial Tx Pathway for Definite ACS

QuickQuiz

- In what situation is a negative myoglobin test useful?
- In what situation is a positive myoglobin test useful?
- What are the pre-emergency department guidelines for chest pain?
- Explain the early risk stratification that occurs in the ED.
- Based on early risk stratification of ACS, to what 3 groups can a patient be assigned?

High-risk features include all of the following:

- Ongoing chest pain for longer than 20 minutes
- Reversible ST-segment changes of at least 0.5 mm
- Elevated cardiac enzymes
- Signs of LV dysfunction

What happens next depends on the ECG:

- If the ECG is abnormal: Follow guidelines (see below).
- If the ECG is nondiagnostic: Repeat the ECG q 15–30 minutes or do continuous monitoring.

Note: An acute MI involving the left circumflex can still present as a nondiagnostic 12-lead ECG; consider obtaining V7–V9 leads.

Based on this early risk stratification, assign patients to one of the following 3 groups in the ACC/AHA protocol:

1) Non-cardiac diagnosis or chronic stable angina: Treat accordingly.
2) Possible ACS with nondiagnostic ECG and normal initial serum markers (Figure 5-2): Observe (at least 12 hours following symptom onset) patients whose presentation suggests ACS, but who are not currently symptomatic, have negative initial cardiac markers, and who have a nondiagnostic initial ECG. After at least 12 hours from symptom onset, if these patients have no recurrence of symptoms, a 2nd set of markers are negative, and an ECG is unchanged, perform further risk stratification with an appropriate stress study. Patients who have a negative or low-risk stress study can be discharged to home and followed as outpatients (green box in Figure 5-2). If the patients who are observed have recurrent symptoms, subsequent positive cardiac markers, ECG changes, or a positive stress study, admit and manage according to the acute ischemia pathway (Figure 5-4).
3) If the initial risk stratification definitely indicates the presence of an ACS, immediately determine whether there is ST-segment elevation or depression on the ECG (Figure 5-3):
   - Admit patients with ST-segment depression and treat according to the acute ischemia protocol.
   - Consider patients with ST-segment elevation or new LBBB for emergent reperfusion therapy.

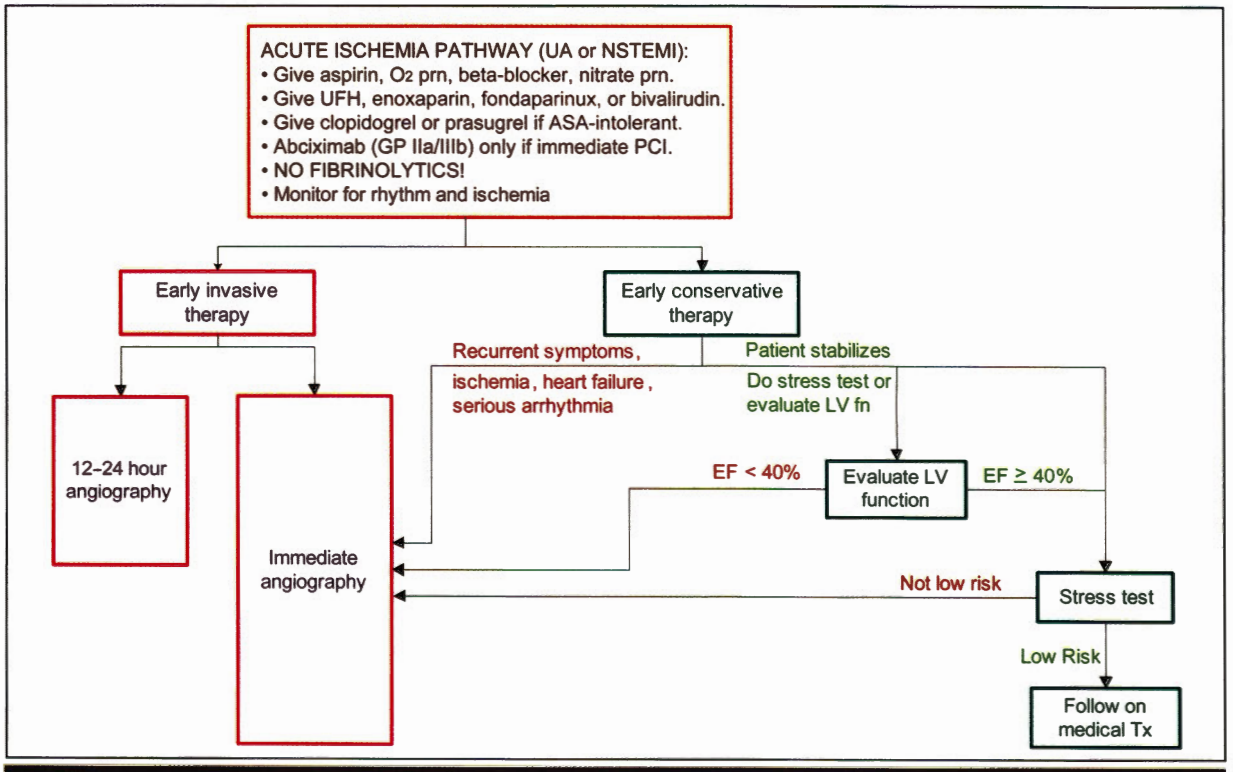


Figure 5-4: Acute Ischemia Treatment Pathway — UA or NSTEMI

We will discuss each of these scenarios shortly, but first let's talk about general measures considered for all patients with ACS.

ACS: GENERAL MEASURES

ECG, NTG, Morphine, Beta-blockers, ACEIs, Atropine

General anti-ischemic measures for all patients with ACS include: continuous ECG monitoring, aspirin, sublingual nitroglycerin (NTG) x 3 prn for pain, and IV NTG for continued ischemia or hypertension. Supplemental oxygen (if oxygen saturation < 90%), morphine if pain is not relieved by NTG, a beta-blocker and an ACE inhibitor if the patient is still hypertensive or has evidence of LV dysfunction (EF < 40%).

Note: Beta-blockers reduce myocardial O_2 consumption. Also, by blocking the often-excessive sympathetic activity, they reduce the load on the heart and decrease the likelihood of arrhythmias. Oral use is preferred and IV use is contraindicated except in special circumstances managed by a cardiologist.

Contraindications to beta-blockers include bradycardia, hypotension, 2nd or 3rd degree AV block, pulmonary edema, and asthma. Note that diabetes is not a contraindication. Caution should be used in giving beta-blockers to patients with signs of acute heart failure. (See more on page 5-47, Treatment for HF, Beta-blockers).

Non-dihydropyridine calcium channel blockers (verapamil or diltiazem) can be given if beta-blockers are contraindicated and the patient continues to have ischemia and hypertension but no LV dysfunction.

Atropine is indicated for the temporary management of acute sinus bradycardia with signs of low cardiac output while preparing for temporary pacing. Bradycardia associated with MI (usually inferior MI) may be temporary, and atropine alone may be sufficient.

Anticoagulant / Antiplatelet Therapy in ACS

Overview

Intense antiplatelet and parenteral anticoagulant therapy with multiple agents is a major treatment recommendation for ACS.

Parenteral Anticoagulants

The parenteral anticoagulants are unfractionated heparin (UFH), enoxaparin, fondaparinux, and bivalirudin. One of these agents is recommended for most patients with ACS. Keep in mind the following:

- Enoxaparin is good but requires discontinuance 12–24 hours before coronary artery bypass surgery (CABG), so UFH is preferred if CABG is anticipated within 24 hours (or coronary angiography, although this is not as absolute). Use caution if advanced renal impairment is present (or use UFH).
- Fondaparinux can be considered if patient has increased risk of bleeding, especially if a conservative (noninvasive) strategy is chosen for the patient. It is not used if percutaneous coronary intervention (PCI) is expected (increased guiding catheter thrombosis and increased coronary complications). If it is in use, and invasive angiography/PCI is planned, switch to another agent, such as UFH or bivalirudin.

Antiplatelet Therapy

Aspirin

Administer aspirin at a dose of 162 or 325 mg immediately to all patients with ACS, and continue indefinitely unless there are contraindications.

Thienopyridines — Platelet $P2Y_{12}$ Receptor Blockade

Thienopyridines include clopidogrel (Plavix®), ticlopidine (Ticlid®), and prasugrel (Effient®). Their effect is additive to aspirin. These drugs block the ADP receptor $P2Y_{12}$ on platelets. Ticlopidine is no longer routinely used due to its side effect profile.

Interaction between PPIs and thienopyridines was thought to be a problem, but latest studies have not proven a cause and effect relationship.

Clopidogrel requires a liver enzyme (CYP2C19) to become active. 2–14% overall are poor metabolizers: 2–5% of African-Americans and Caucasians and up to 20% of Asians. There are genetic tests that can check for this issue. In 2010, Plavix® received an FDA boxed warning about poor metabolizers and the tests available, but genetic testing is not recommended in any current guideline.

Prasugrel is a thienopyridine that has a faster onset of action and is effective in clopidogrel-resistant patients. It has significantly more antiplatelet activity and therefore lower cardiovascular events—but also higher rates of significant bleeding and is contraindicated in the elderly.

Clopidogrel and prasugrel are now used interchangeably for all proven ACS scenarios except if CABG is imminent (operative bleeding complications).

Non-thienopyridines

Ticagrelor (Brilinta™), a non-thienopyridine, is a recently approved reversible oral antagonist of the $P2Y_{12}$ receptor with a rapid onset of action. This has proven equivalent to prasugrel (similarly more effective but with more bleeding than clopidogrel) and is quickly being added to guidelines as an alternative for clopidogrel/prasugrel.

Glycoprotein (GP) IIb/IIIa Inhibitors

GP IIb/IIIa inhibitors act on the final common pathway of platelet aggregation—where fibrin binds platelets together by connecting to the GP IIb/IIIa receptor. The

Quick Quiz

- Okay, the patient has ACS. What anti-ischemic measures are done initially for all patients with ACS?
- Which patients should receive a platelet GP IIb/IIIa inhibitor?
- Of those with ACS, what group gets considered for fibrinolytic therapy and what group definitely does not?
- Under what conditions is angiography/PCI considered for those with UA/NSTEMI?

most studied drug is abciximab. Others are eptifibatide, tirofiban, and lamifiban. Only the IV forms are effective. GP IIb/IIIa inhibitors are considered for high-risk ACS patients with elevated troponin (i.e., instability, dynamic ECG changes) if going immediately to cath lab for probable PCI.

Fibrinolytic Therapy in ACS

Do not give fibrinolytic therapy to patients with UA/NSTEMI because it increases mortality. Do give fibrinolytic therapy to those ACS patients with STEMI or new LBBB if immediate PCI is not available and if there are no contraindications (discussed later).

Antiarrhythmic Drugs in ACS

Give lidocaine only if the patient has V-fib/tach. Prophylactic lidocaine is harmful. Lidocaine has an increased half-life in patients with CHF and those on propranolol. Amiodarone is the current drug of choice for ventricular tachycardia and ventricular fibrillation.

ACS: MANAGEMENT OF UA/NSTEMI —THE ACUTE ISCHEMIA PATHWAY

Early Invasive vs. Conservative Therapy

Note: The 2011 update of the ACC/AHA UA/NSTEMI treatment guidelines have 2 areas of focus (Figure 5-4 on page 5-15):

1) Antithrombotic therapy with multiple agents
2) Aggressive use of early cardiac catheterization in those with moderate-to-high risk

Regarding UA/NSTEMI treatment:

- Use antiplatelet therapy, such as clopidogrel or prasugrel for at least 1 year after receiving a drug-eluting stent and for up to a year without a stent or with a bare metal stent.
- Intense lipid and BP control is recommended.
- Stop all nonsteroidal antiinflammatory drugs (NSAIDs)—except ASA— during hospitalization.

Okay, you have determined the patient is having ACS and have initiated treatment according to the general measures on page 5-16. You've drawn labs and done the ECG, which reveals no acute ST changes. The labs come back, and you now determine that the patient has NSTEMI (cardiac markers abnormal) or UA (markers normal).

You now have 2 options:

1) Early invasive therapy (angiography)
2) Early conservative therapy

Early Invasive Therapy in UA/NSTEMI

Urgent invasive therapy for UA/NSTEMI indications:

- CHF or hemodynamic instability
- Recurrent or refractory angina
- Life-threatening arrhythmias

Invasive therapy for UA/NSTEMI within 12–24 hours indications:

- Elevated cTnI or cTnT
- Dynamic ST changes
- Diabetes
- GFR < 60 mL/min
- EF < 40%
- Early post-MI angina
- PCI within the previous 6 months
- Prior MI
- Prior CABG
- Intermediate/high-risk patients (either by clinical judgment or using a scoring system such as the TIMI risk score)

All UA/NSTEMI patients selected for early invasive therapy get the following medical therapy:

- Parenteral anticoagulant:
  - UFH, enoxaparin, or bivalirudin. Do not give fondaparinux due to increased rate of catheter thrombus formation. Give UFH or bivalirudin if going to cath lab within 24 hours.
- Antiplatelet therapy:
  - ASA plus either clopidogrel or prasugrel (dual therapy).
  - IIb/IIIa inhibitor can be given if the patient is high risk and immediately going to the cath lab for probable PCI.

Remember: UA/NSTEMI patients do not receive fibrinolytic therapy.

Early Conservative Therapy in UA/NSTEMI

Patients with UA/NSTEMI who respond to intense medical therapy, who have none of the high-risk features listed under invasive therapy above, and who do well on post-ACS stress testing are at low risk for immediate and 1-year mortality—and can be followed without invasive evaluation.

Conservative therapy for UA/NSTEMI patients:

- Parenteral anticoagulant:
  - UFH, enoxaparin, or fondaparinux. Fondaparinux is especially useful if there is risk of bleeding.
- Antiplatelet therapy:
  - ASA with either clopidogrel or prasugrel. Always give dual antiplatelet therapy.
  - IIb/IIIa inhibitors are not given for conservative therapy. It is reserved for those immediately going to the cath lab for probable PCI.

This is basically the same anticoagulant/antiplatelet treatment as those getting UA/NSTEMI early invasive therapy, except that IIb/IIIa inhibitors are not used and fondaparinux is now a reasonable option.

Again, remember that UA/NSTEMI patients do not receive fibrinolytic therapy.

Long-term Antiplatelet Therapy after UA/NSTEMI

Antiplatelet treatment without a stent:

- ASA 75–162 mg/d for life
- Clopidogrel (or similar agent) x 1 month to 1 year

Bare metal stent (BMS):

- ASA 162–325 mg/d x 1 month, then 75–162 mg/d for life
- Clopidogrel (or similar agent) x 1 month to 1 year

Drug-eluting stent (DES):

- ASA 162–325 mg/d for 3–6 months, then 75–162 mg/d for life
- Clopidogrel (or similar agent) for at least 1 year. Consider continuing for longer than a year.

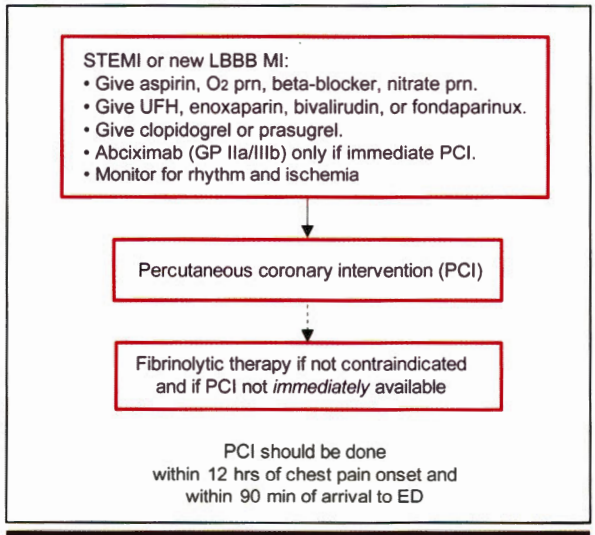


Figure 5-5: Acute MI Treatment Pathway with STEMI or New LBBB

Cocaine and Methamphetamine Users with ST Elevation

Give NTG and calcium channel blockers (not beta-blockers). In addition:

- If ST-segments are elevated and patient is not better, go to cath immediately if possible.
- If ST-segments are elevated, cath not available, and still symptomatic after NTG and calcium channel blockers, then give fibrinolytics.
- Do not go to cath if no ST-segment or T-wave changes and with negative stress test and negative biomarkers.
- Avoid beta-blockers.

ACS: MANAGEMENT WITH STEMI *OR* NEW LBBB

Note

The management of acute coronary syndrome (ACS) for those with STEMI is the same as for those with a new LBBB (Figure 5-5). Also know that STEMI includes those with a posterior infarct (ST depression in V1, V2 and tall Rs in V1, V2). General measures are discussed above.

The following are additions to the general measures for all ACS patients discussed on page 5-16.

STEMI (or new LBBB) patients get the following medical therapy:

- Parenteral anticoagulant:
  - UFH, enoxaparin, or bivalirudin. Give UFH or bivalirudin if going to cath lab within 24 hours (which should ideally be nearly everybody).
- Antiplatelet therapy:
  - ASA plus clopidogrel or other agent (dual therapy)
  - IIb/IIIa inhibitors as early as possible when patients are going to the cath lab for PCI

This is very similar to the anticoagulant/antiplatelet treatment in those getting UA/NSTEMI therapy.

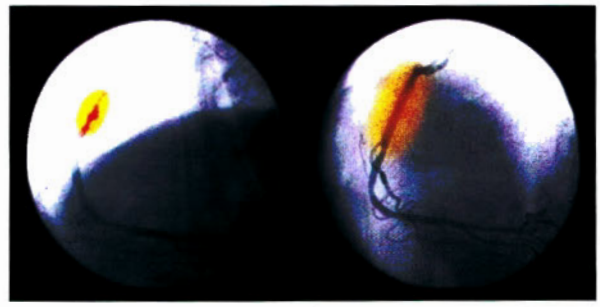


Image 5-5: Angiogram of a blocked coronary artery before and after stent placement

Quick Quiz

- What are the reperfusion therapies you give to (or consider for) those with STEMI or new LBBB? Who gets what?
- In what conditions has PCI been shown to be better than fibrinolytic therapy?
- What are the absolute and relative contraindications to fibrinolytic therapy?
- In what conditions has PCI been shown to be especially indicated?

Immediate Reperfusion Therapies

Overview

Consider emergent reperfusion (primary PCI or fibrinolytic therapy) in all patients who present with a STEMI or a new (or presumed new) left bundle-branch block.

Primary PCI

Primary percutaneous coronary intervention (PCI) is urgent reperfusion therapy typically using a stent (Image 5-5).

Primary PCI has been shown to be better than fibrinolytic therapy in establishing normal flow in the affected (culprit) coronary artery when used in patients with STEMI, MI with new LBBB, and new true posterior MI. Outcomes are also better than fibrinolytic therapy as long as an experienced practitioner performs the procedure within 12 hours of the onset of symptoms—and within 90 minutes of the arrival of the patient in the ED. (Door-to-balloon time is a commonly measured metric for quality of care in STEMI.)

Primary PCI is particularly indicated in patients who develop cardiogenic shock following a STEMI or new LBBB MI.

PCI has been shown by several studies to result in a substantially greater proportion of patent infarct-related arteries than occurs with fibrinolytic therapy.

Coronary angiography, following a STEMI or a new bundle-branch block MI that is initially treated medically, is indicated if the patient has persistent or stuttering episodes of ischemia (including on post-MI stress testing), with or without ECG changes. Also do angiography in the medically treated group if they develop pulmonary congestion or shock.

PCI of the left main coronary artery using stents can be an alternative to CABG in patients:

- at high surgical risk, and
- low risk for complications with stent placement.

Fibrinolytic Therapy

If primary PCI is not available within 90 minutes of arrival, initiate fibrinolytic therapy in STEMI patients:

- who have ST-segment elevation in ≥ 2 contiguous ECG leads or new LBBB, and
- who present within 12 hours of the onset of symptoms.

Many studies show that the sooner the patient receives fibrinolytic therapy, the greater the benefit in reduction of mortality, with the most benefit in the first 4 hours and the greatest of all in the first hour. Patients with new bundle-branch block benefit the most, followed by anterior MI, then inferior MI. Start fibrinolytic therapy within 30 minutes of arrival in the ED.

Note: Fibrinolytics are used for patients at facilities that do not have the capabilities for urgent PCI. According to the 2009 ACC/AHA Joint STEMI/PCI guidelines focused update, following treatment with fibrinolytic therapy, high-risk STEMI patients should be transferred to a PCI center to undergo coronary angiography and PCI immediately—without waiting to determine whether reperfusion has occurred.

Fibrinolytic agents include the recombinant, tissue-type plasminogen activators (e.g., rt-PA, TNK), anistreplase, streptokinase, and urokinase.

TNK is a recombinant mutant of rt-PA that has more fibrin selectivity and a longer half-life than rt-PA.

Contraindications to fibrinolytic therapy can be either absolute or relative contraindications.

Absolute contraindications:

- Previous hemorrhagic stroke at any time; other cerebrovascular events within 1 year
- Intracranial neoplasm
- Active internal bleeding
- Suspected aortic dissection

Relative contraindications:

- Persistent BP > 180/110
- Remote non-hemorrhagic CVA (> 1 year)
- Current use of anticoagulants with INR > 2–3; bleeding diathesis
- Recent (2–4 weeks) major trauma or surgical procedure
- Noncompressible vascular puncture
- Previous exposure to streptokinase/anistreplase
- Pregnancy
- Active peptic ulcer

Of the patients with STEMI/new LBBB initially evaluated for fibrinolytic therapy, almost 2/3 do not get fibrinolytic therapy for the reasons listed above or because of advanced age. The risk of intracranial

hemorrhage increases with age, to as much as 1% in patients > 75, but age by itself is no longer a contraindication. Many of these patients are still good candidates for primary PCI.

Notes Regarding Guidelines

- Stop all NSAIDs (except ASA), including COX-2s!
- Start oral beta-blocker within 24 hours.
- Do not give full-dose fibrinolytic therapy if immediate PCI is anticipated.
- Clopidogrel or similar agent is added to ASA for at least 14 days for all STEMIs—up to a year for most!
- LDL should be < 100 for all, and many recommend < 70.
- ACE inhibitors for all who can tolerate are given post-procedure.
- IV nitroglycerin in the first 24 hours for ongoing chest pain, hypertension, or hypertension.
- Blood sugars must be maintained at < 180 using insulin-based regimens for diabetics while avoiding hypoglycemia.
- Influenza vaccine yearly.

In the ACC/AHA 2009 focused updates on STEMIs, prasugrel and bivalirudin were incorporated into STEMI treatment (as noted above).

If CABG is planned, clopidogrel should be stopped at least 5 days before and prasugrel stopped 7 days before surgery.

Complications of Myocardial Infarction

Left Ventricular Dysfunction

Left ventricular dysfunction after an MI is predictive of a poor prognosis. Pump failure is now the primary cause of in-hospital death from STEMI. Patients in cardiogenic shock have historically had mortality rates of > 85%, but studies using PCI or emergent CABG have demonstrated an improvement in these dismal outcomes.

Right Ventricular Infarction Complications

Right ventricular infarction (RVI) frequently accompanies an inferior MI and is almost always due to occlusion of the proximal right coronary artery. Inferior MI complicated by RVI has a significantly worse prognosis than inferior MI alone.

ST-segment elevation in right-sided chest leads (e.g., V3R–V7R) is an indication of inferior/posterior infarctions of the right ventricle. If a patient with inferior MI presents with hypotension, suspect RVI.

Suspect RVI in all cases of inferior MI, which is typified by the clinical triad of hypotension, clear lung fields, and elevated jugular venous pressure. A Kussmaul sign is frequently present.

If you perform right heart catheterization, an elevated RA pressure of ≥ 10 mmHg and > 80% of the pulmonary capillary wedge pressure (PCWP) are quite specific for right ventricular MI.

Management of RVI is frequently diametrically opposed to that of LV infarction. Avoid nitrates and preload reducing agents. Fluid support is essential. Inotropic support, usually with dobutamine, may be necessary.

Arrhythmias and Blocks

A variety of tachyarrhythmias can occur with myocardial infarction/ischemia.

Atrial fibrillation with hemodynamic instability requires emergent treatment with DC synchronized cardioversion. If patients do not require cardioversion, control the ventricular rate in these patients with beta-blockers, diltiazem, or digoxin.

For sustained ventricular tachycardia (VT) with a pulse accompanied by hemodynamic instability, treat with DC synchronized cardioversion.

Treat ventricular fibrillation (VF) and pulseless VT with defibrillation (unsynchronized DC cardioversion).

For episodes of sustained VT not associated with hemodynamic instability:

- Amiodarone is the drug of choice. It can be given as a continuous infusion or as boluses every 10–15 minutes. Lidocaine can be an effective alternative agent, and procainamide is also an option.
- Correct any hypokalemia or hypomagnesemia.
- Routine prophylactic use of lidocaine to prevent VT is no longer recommended.

For patients who develop ventricular tachycardia or ventricular fibrillation after the first 48 hours, the short-term and long-term mortality rates are increased. Such patients should be considered for electrophysiologic study and implantation of a cardioverter/defibrillator (ICD).

Note that patients with isolated, premature ventricular contractions, or runs of nonsustained VT, do not need antiarrhythmic therapy on a routine basis. Beta-blockers are effective for ventricular ectopic activity and preventing arrhythmias.

Bradycardia and AV block are more common with inferior MIs than anterior MIs because of the increased vagal tone and AV nodal ischemia associated with an inferior infarct. Remember: Prognosis is related to the size of the infarct, not the presence of AV block itself. The block is often transient and does not require a permanent pacemaker.

However, AV block accompanying an anterior MI implies destruction of a large amount of myocardium in the interventricular septum, is associated with a high mortality, and frequently requires permanent pacing if the patient survives.

Quick Quiz

- How does management of a RV infarction differ from LV infarction?
- Which patients with ventricular tachycardia after an MI get DC cardioversion?
- What are the medical options for hemodynamically stable MI patients with VT?
- When do the major mechanical complications tend to occur after an MI? How do they present?
- What are the primary risk factors for CAD?
- What increases HDL?

Indications for temporary pacing at the time of an MI include:

- Asystole or sinus arrest
- Complete (third-degree) AV block
- Mobitz type II second-degree AV block
- Symptomatic bradycardia (includes sinus bradycardia with hypotension and type I second-degree AV block with hypotension not responsive to atropine)

Mechanical Complications after STEMI

Rupture of a papillary muscle, if it occurs, usually does so 3–7 days after an inferior MI. The patient rapidly develops shock and acute pulmonary edema. You may (or may not) hear a short, early systolic murmur. Echocardiography is indicated in any hemodynamically unstable MI patient and is the diagnostic modality of choice for all of these conditions. The treatment is urgent cardiothoracic surgery.

Ventricular septal defect, if it occurs, usually does so 3–7 days after an anteroseptal MI. Incidence is about 0.3% of MIs (before reperfusion therapy era, incidence was 1–3%). Again, the patient rapidly develops shock. A loud, holosystolic murmur is heard widely over the precordium. Samples from a right heart catheter demonstrate an oxygen saturation step-up from the right atrium to the pulmonary artery of at least 10%. Confirm the diagnosis by echocardiography. Once again, the mortality rate is very high, and the only treatment is urgent cardiothoracic surgery.

Free-wall rupture of the LV usually occurs 3–7 days after a large, anterior MI, most frequently in elderly hypertensive women. Sudden syncope is typical. The neck veins are grossly engorged from tamponade; pulsus paradoxus, tachycardia, and hypotension make up the triad. Hemodynamic collapse occurs quickly. There have been a few heroic saves with immediate surgery, but rapid death is the usual outcome.

Invasive Hemodynamic Devices

The ACC/AHA guidelines on the management of STEMI recommend the insertion of a pulmonary artery balloon flotation catheter in patients with cardiogenic shock or a suspected mechanical complication of an MI. However, most of the information that could be obtained by this device can now be acquired by echocardiography, and the use of pulmonary catheters has declined dramatically. Arterial pressure monitoring with an indwelling arterial line is appropriate in some patients, particularly those requiring mechanical ventilation. Intraaortic balloon counterpulsation is indicated in patients in cardiogenic shock or with a mechanical complication as a bridge to urgent revascularization and/or surgery.

Implantable Cardioverter-Defibrillators

Studies have shown that implantable cardioverter-defibrillators (ICD) prolong survival in post-MI patients with LVEF < 35%. LVEF is typically re-evaluated after 40 days following revascularization to allow stunned or hibernating myocardium to recover. An ICD is particularly indicated if there are baseline episodes of ventricular tachycardia.

CORONARY ARTERY DISEASE

OVERVIEW

We'll talk about the risk factors for CAD, screening, and revascularization options.

RISK FACTORS FOR CAD

The primary risk factors for CAD:

- Age
- Male gender
- Family history of early CAD
- Smoking
- Hypertension
- DM
- Elevated LDL level

Aerobic exercise and elevated HDL are inversely linked to CAD. HDL is increased by exercise, estrogens, niacin, and small amounts of EtOH. HDL is decreased by smoking and androgens.

SCREENING

Check a "fasting lipid panel" at least every 5 years in healthy persons, starting at age 20. The "fasting lipid panel" includes total cholesterol, LDL, HDL, and triglycerides. Much more on lipids in the Endocrinology section, Book 4!

LDL is usually a calculated value:

LDL = total cholesterol – HDL – 1/5 of triglycerides

LDL treatment goals are assigned correspondingly in proportion to an individual's predicted risk for future MI or death (typically estimated via a scoring system such as the Framingham Risk Score), as follows:

- Low risk (0–1 risk factor): < 160
- Moderate risk (≥ 2 risk factors, 10-year risk < 20%): < 130
- High risk (documented CAD, DM, or 10-year risk > 20%): < 100
- Based on recent large clinical trial data, there is an optional, more aggressive treatment goal of LDL: < 100 for those at moderately high risk (10-year risk = 10–20%) and < 70 for highest risk individuals. Know of its existence, although you will be more likely to be asked about the standard goals.

Lipids may be falsely low for up to 2 months after a myocardial infarction or cardiac surgery.

Statins enhance plaque stabilization and may independently improve long-term prognosis.

NCEP guidelines and drug treatment are covered in the Endocrinology section, Book 4, under Lipoproteins.

Cardiologists feel that once LDL is treated to goal, non-HDL cholesterol (i.e., triglycerides) should be targeted next.

Additional factors to consider:

- Advise no smoking.
- Give antihypertensive medications to treat to goal BP.
- Coronary artery calcium scores and other serum markers, such as high sensitivity CRP, can be used in some patient populations to add to the total risk assessment for coronary artery disease.
- Do not forget to ask about substance abuse, particularly cocaine.

REVASCULARIZATION

The revascularization options are:

- Coronary artery bypass graft (CABG)
- Percutaneous coronary intervention (PCI) with either stents or angioplasty

CABG vs. PCI

The ACC/AHA guidelines recommend revascularization under the following circumstances:

- CABG for all patients with significant, left main CAD or left main equivalent (i.e., proximal left anterior descending [LAD]) plus proximal circumflex with favorable anatomy.
- CABG for all patients with 3-vessel disease; the survival benefit is greater in patients with abnormal LV function (EF < 50%).
- CABG for all patients with 2-vessel disease and significant proximal left anterior descending CAD and either abnormal LV function (EF < 50%) or demonstrable ischemia on noninvasive testing.
- PCI or CABG for patients with 1- or 2-vessel CAD without significant, proximal left anterior descending CAD, but with a large area of viable myocardium and high-risk criteria on noninvasive testing.
- PCI for patients with multi-vessel coronary disease with suitable coronary anatomy, with normal LV function, and without diabetes.

CABG improves symptoms and survival in:

- Left main disease or left main equivalent (2-vessel disease with 1 vessel being proximal LAD)
- 3-vessel disease with LV dysfunction
- Diabetics

If there is no left main or proximal LAD involvement, CABG improves the symptoms of angina in stable 1- and 2-vessel disease but does not affect patient survival!

With saphenous vein bypass, there is a 50% chance of occlusion in 10 years (about 5% per year), but with internal mammary grafts, 90% are open at 10 years! Internal mammary grafts are the standard of care for surgical revascularization of the LAD. Chance of MI is the same after bypass.

CABG vs. PCI: In most of the recent trials, patients have the same survival results, but the need for revascularization is greater in the PCI group. In these trials, survival has been better for diabetics who get an internal mammary-LAD bypass than for those with a PCI. Studies are continually trying to tease out specific patient populations and coronary lesions that benefit from CABG vs. PCI, particularly in the drug-eluting stent era. This is a "moving target" because left main disease may be stented as well now with good results in certain patient groups.

Again: Survival does not improve after bypass unless the patient has:

- 3-vessel disease with significant LV dysfunction, or
- left main or left main-equivalent disease, or
- diabetes.

Stents

Stents are the mainstay of PCI. These are placed in the area of blockage and then expanded, thereby opening the lumen to normal size. Stents do not cause as much dissection of the plaque and are not susceptible to elastic recoil—both of which can occur with angioplasty alone. Stents also have a lower restenosis rate than plain angioplasty. The in-stent restenosis is almost always due to neointimal hyperplasia, but stents also carry a risk of in-stent thrombosis,

Quick Quiz

- Which patient groups definitely should get CABG?
- Which patient group should definitely get PCI?
- In 3-vessel disease, what is the benefit of CABG—survival, symptoms, or both?
- In 1-vessel disease, what is the benefit of CABG—survival, symptoms, or both?
- Name 2 drugs used with drug-eluting stents.
- What is Buerger disease?
- What are the causes of arteriosclerotic peripheral vascular disease?
- What is the difference between claudication and pseudoclaudication?

particularly during the early period after placement. This is why antiplatelet therapy is so important after stent placement, and a bare metal stent requires dual antiplatelet therapy for a minimum of 30 days to prevent in-stent thrombosis.

Drug-eluting stents (DESs) are made with a metallic stent backbone supporting a polymer covering that contains a slow-release drug. These drugs have properties that decrease the neointimal hyperplasia that is the cause of most restenoses. Commonly used DESs contain medications such as sirolimus, paclitaxel, and everolimus. With these agents, the restenosis rate drops dramatically (to 5%) compared to bare metal stents (25%), although there is a slight increase in late stent thrombosis (0.4%). As opposed to bare metal stents, DESs require prolonged obligatory dual-antiplatelet therapy due to the delay in neointimalization: minimum 1 year as opposed to 30 days with a bare metal stent. There are growing concerns over late stent thrombosis with DES, particularly after antiplatelet agent withdrawal. Also, rare local and systemic hypersensitivity reactions have been reported and may contribute to late stent thrombosis risk. Thus, prolonged antiplatelet therapy is needed > 1 year.

Other

Balloon angioplasty stretches the plaque and vessel wall to enlarge the lumen. There is a 30–50% chance of restenosis within 6 months. Balloon angioplasty is currently used for vessels too small to allow coronary stenting. It is also used to pre-dilate vessels before stent placement.

Rotational ablation atherectomy (catheter with diamond-grinding chips in it) has a role for heavily calcified lesions.

PERIPHERAL ARTERIAL DISEASE

CAUSES OF PAD AND INTERMITTENT CLAUDICATION

Peripheral arterial disease (PAD), previously called peripheral vascular disease (PVD), has many causes, including the following:

- Arteriosclerosis (arteriosclerosis obliterans—most common cause in middle-aged and older); 2 major risk factors for arteriosclerotic PAD are diabetes (5x greater chance) and smoking. Other modifiable risk factors include hyperhomocysteinemia, hyperlipidemia, and hypertension. Note: Patients with arteriosclerotic PAD are at increased risk of MI and stroke.
- Arteritis (connective tissue disease, Takayasu arteritis).
- Trauma (jackhammer hands).
- Buerger disease (esp. smoking males < 30 years old)—also called thromboangiitis obliterans. It involves medium and small arteries and often affects arteries of the wrists (positive Allen test) and hands.
- Entrapment—think especially of thoracic outlet syndrome and popliteal artery entrapment. Suspect popliteal artery entrapment in young men with intermittent claudication of calf or foot arch with walking—but not running!

It is important to differentiate vascular claudication from lumbar spinal stenosis, and know that the latter causes a pseudoclaudication. Lumbar spinal stenosis is relieved only by sitting down (flexing the spine), but not by standing still. It is exacerbated by anything that extends the spine, such as standing or walking (especially downhill). Vascular claudication is relieved by sitting down or standing still. Neither disease causes nocturnal leg cramps. When the distance to onset of claudication or severity abruptly changes, thrombosis *in situ* or an embolic event should be considered.

DIAGNOSIS OF PAD

PAD is defined as a charted or screening ankle-brachial index (ABI) of < 0.90. ABI before and after exercise is the best test of the degree of functional impairment in PAD. In severe disease, the ankle pressure can fall to undetectable levels after exercise.

Doppler and duplex ultrasound imaging are noninvasive methods of visualizing the artery and arterial blood flow.

Arteriography is the best test for defining the location of the disease. CT and MR angiography using new generation scanners give outstanding images without the need for arterial access.

Thromboembolism is the usual problem with aneurysms of limb arteries. Aneurysm of the popliteal artery can be diagnosed by U/S or CT scan.

TREATMENT OF PAD

Four noninvasive interventions decrease the symptoms of intermittent claudication due to arteriosclerosis:

1) Stopping smoking.
2) Regular exercise (30 minutes daily).
3) Cilostazol (Pletal®), a phosphodiesterase inhibitor that increases the cAMP in platelets and blood vessels—resulting in a reversible inhibition of platelet aggregation. It has been shown to increase maximum walking distance. Use only if LV function is normal because patients with class III or IV heart failure have increased mortality with any phosphodiesterase inhibitor.
4) Pentoxifylline (Trental®).

These patients should also have aggressive BP control and be treated with statin therapy to goal LDL levels. Antiplatelet therapy with aspirin or clopidogrel is indicated as well to decrease cardiovascular events.

If PAD is due to Buerger disease, stop tobacco use. If Takayasu arteritis is present, treat the disease with steroids.

Other treatment: Many forms of PAD can now be effectively treated with percutaneous intervention (angioplasty and stents)—with low restenosis rates. Surgical bypass can also effectively relieve symptoms and ischemia. In general, proximal (iliac) stenosis and short-segment occlusions are best treated endovascularly, with long lesions and occlusions best treated surgically.

With acute peripheral arterial occlusion, heparin protects the collateral circulation during evaluation by preventing thrombus formation around the new clot. Many arterial emboli to the lower extremities come from the heart, but atheromatous emboli from a diseased aorta may also occur, which can cause renal failure and ischemia of the toes (Image 5-6). Embolectomy/thrombectomy is the treatment of choice.

Hoptoto Associates Photo Researchers, Inc.

Image 5-6: Thromboangiitis obliterans or Buerger disease symptoms on patient's toes

VASOSPASTIC DISEASE

Vasospastic disorders: Primary Raynaud syndrome is constriction of small arteries and arterioles when cold, leading to acrocyanosis. It is sometimes associated with livedo reticularis. It involves small arteries and arterioles in the digits and skin (Image 5-7).

Treatment: calcium channel blockers, biofeedback, and nitroglycerin if CCBs are ineffective.

Prinzmetal angina is a coronary artery vasospastic disease that can lead to transient, dramatic ST elevation mainly at rest and occasionally with exercise. Think of this diagnosis in a younger individual with transient ST elevation during an episode of pain but normal coronary arteries on cath. Treatment includes nitrates and especially calcium channel blockers.

CAROTID ARTERY DISEASE

CAROTID ARTERY ATHEROSCLEROSIS

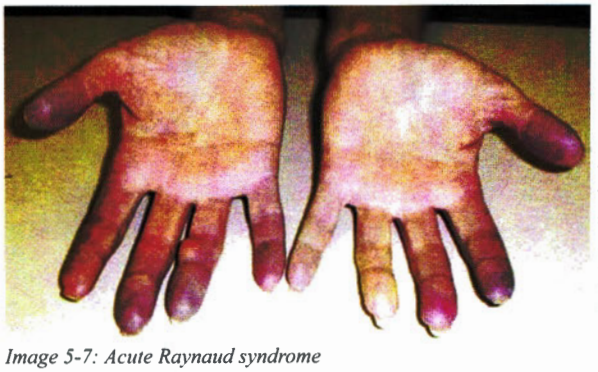
Atherosclerosis within the carotid artery occurs most frequently within the common carotid bifurcation and proximal internal carotid artery. Patients with atherosclerotic carotid artery disease are at a higher risk of having an MI than of having a TIA or stroke! Although the benefit is uncertain, most clinicians do noninvasive testing on patients with an asymptomatic carotid bruit. But, if symptomatic (i.e., TIAs), carotid ultrasound is definitely indicated.

Carotid endarterectomy is indicated for critical lesions (> 70% stenosis). Carotid stenting is emerging as a useful tool for patients who are high risk for surgical endarterectomy.

Medical therapy for atherosclerotic carotid disease includes aspirin or clopidogrel.

INTERNAL CAROTID ARTERY DISSECTION

Suspect spontaneous dissection of the internal carotid artery (cervical area) in a patient with unilateral headache associated with either TIAs or a dilated pupil. It can



International Scleroderma Network(ur-sclero.org)

Image 5-7: Acute Raynaud syndrome

QuickQuiz

- What are the 4 noninvasive interventions that decrease intermittent claudication due to arteriosclerosis?
- Atherosclerotic disease of the carotid artery provides more risk for which of these: MI, stroke, or TIA?
- When is carotid endarterectomy indicated?
- What is the prognosis for spontaneous dissection of the internal carotid artery?

also present with only a history of unilateral neck pain in a hypertensive patient. Look for cholesterol emboli on the funduscopic exam. Spontaneous dissection of the internal carotid artery usually resolves with no treatment, with excellent recovery. Occasionally anticoagulation or a stent is needed.

CEREBRAL EMBOLIC DISEASE

OVERVIEW

The causes of cerebral embolic events of cardiac origin (and the approximate % of events they cause):

- Atrial fibrillation (45%)
- Acute MI (15%)
- Ventricular aneurysm (10%)
- Mechanical valve prosthesis (10%)
- Valvular heart diseases, including endocarditis (10%)
- Other cardiac abnormalities (10%)

"Other" includes patent foramen ovale, which allows an intermittent right-to-left shunt and "paradoxical" emboli, and dilated cardiomyopathy, which allows formation of a mural thrombus.

Non-cardiac cause of embolic cerebral events is atherosclerosis, both aortic and carotid (discussed above).

Non-embolic causes of cerebral ischemic attacks or strokes are thrombosis, systemic hypoperfusion, and blood disorders (especially clotting disorders).

TIA

The definition of transient ischemic attack (TIA) has changed and is no longer related to duration of symptoms. TIA is now defined as any period of CNS ischemia without infarction. Ischemic stroke is defined as ischemia with infarction. The CNS includes the brain, spinal cord, and retina. More on TIA under Vertigo in the Neurology section, Book 5.

Medical treatment of TIA: If there is a history of TIA but no history of cardioembolic stroke, no significant lesion is found, and the patient does not have atrial fibrillation, it is probable that the cause is atherosclerosis; therefore, the patient should be placed on antiplatelet therapy: ASA + dipyridamole, ASA alone, or clopidogrel alone. Ticlopidine is similar to clopidogrel but is not a first-line drug because of severe neutropenia that occurs in 1%! Unlike with coronary artery disease, the combination of ASA + clopidogrel has not been shown to be beneficial for stroke or TIA prevention over either agent alone.

AORTIC DISEASE

AORTIC ANEURYSMS

Overview

The causes of aortic aneurysms may be broadly categorized as degenerative diseases, inherited or developmental diseases, infections, vasculitis, and trauma. With aortic aneurysms, rupture is the biggest threat. Atheroembolism is another complication of abdominal aortic aneurysm. Signs of atheroembolism, in decreasing order, are: livedo reticularis, then blue toes, then ischemic ulceration. (Remember, though, that most emboli to the lower extremities originate in the heart!) Hypertension from progressive renal insufficiency may occur if abdominal aneurysms are not treated.

Thoracic Aortic Aneurysms

Thoracic aortic aneurysms tend to dissect as well as rupture. Aortic dissection is an intimal tear in the aorta, resulting in a dissecting hematoma, which may cause severe pain and occlusion of the aorta and involved vessels. Systemic hypertension, cystic medial necrosis, bicuspid aortic valve, coarctation of the aorta, and 3rd trimester of pregnancy are predisposing factors. Aortic dissection is a major cause of death in those with Marfan syndrome.

Cystic medial necrosis is the most common pathology in ascending aortic aneurysms, whereas atherosclerosis is most frequently associated with aneurysms of the aortic arch and descending thoracic aorta. The average growth rate of thoracic aneurysms is 0.1–0.2 cm per year.

The **DeBakey** classification of aortic dissection lists 3 types:

Type I: Involves the ascending aorta, aortic arch, and descending aorta

Type II: Proximal in the ascending aorta alone

Type III : Involves the descending aorta alone, usually just after the subclavian artery

The **Stanford** classification lists 2 types:

Type A: Any dissection involving the ascending aorta

Type B: Limited to the descending aorta only

Stanford Type A combines DeBakey I and II; this makes sense because all type A aortic dissections are managed similarly. Hence, the Stanford classification is more commonly used now.

Proximal dissection can cause aortic regurgitation, hemopericardium with tamponade, and MI due to involvement of a coronary artery (usually the right coronary artery). Dissections typically present with severe anterior chest pain and/or severe interscapular pain.

Diagnosis [Know]: CT and MRI are the diagnostic procedures of choice for possible aortic dissection. Transesophageal echo is a reasonable alternative if the patient is too unstable to go to radiology.

Treatment: Decrease elevated blood pressure immediately with beta-blockers and nitroprusside. There is preliminary evidence that Marfan's-related aneurysms should be treated with an ACEI or ARB to block TGF- signaling. Ascending aortic dissections are at greater risk for complications, so they always require surgery. Descending aortic dissections are usually treated medically unless evidence of end-organ damage develops (renal insufficiency, GI ischemia, limb compromise), which suggests continuing dissection and the need for emergent surgery.

Thoracic aortic aneurysm: Surgery is indicated at 5.5 cm in the ascending aorta (5 cm if Marfan's) and 6 cm in the descending aorta.

Also, surgery is indicated if the aneurysm is small but enlarging rapidly (>10 mm in a year), associated with symptoms, compressing surrounding structures, or is of traumatic origin.

Abdominal Aortic Aneurysm (AAA)

Screening is covered in the General Internal Medicine section, Book 5, under Screening Exams.

AAAs are more common in men. They tend to rupture rather than dissect. If asymptomatic, aneurysms 4–5.4 cm should be monitored with ultrasound or CT every 6–12 months. Aneurysms 5.5 cm or greater should undergo surgical repair. AAAs that expand > 0.5 cm in 6 months should undergo surgical repair as well. Put the patient on beta-blockers during the observation period.

Know that acute MI and other CAD-related problems are the cause of 70% of perioperative mortality for AAA repair. Surgical risk is decreased if the patient does not have CAD, so perform a CAD screening with a nuclear stress test if the patient has ≥ 2 CAD risk factors (listed on page 5-21).

Endovascular stenting is less invasive and an effective method of treating AAAs. It has become the most common method of repairing localized infrarenal aneurysms.

COARCTATION OF THE AORTA

Coarctation of the aorta (COA) is a congenital problem that causes persistent hypertension, sometimes even after surgical correction. Cardiac output responds normally to exercise. Blood pressure is higher in the upper extremities than in the lower. People with COA have a high risk of developing subsequent aortic disease, including aneurysms and dissection, even after correction of the lesion. See more on COA on page 5-52.

VALVULAR HEART DISEASE

INFECTIVE ENDOCARDITIS

Overview

[Know this section well.]

More on causes and treatments of infective endocarditis (IE) is discussed in the Infectious Disease section, Book 1. For treatment purposes, the newest method of classification of endocarditis:

- Native valve
- Prosthetic valve
- IV drug related
- Culture negative

These can have acute or subacute presentations.

Streptococcus, *Enterococcus*, and *S. epidermidis* are the usual causes of the subacute form, while *S. aureus*, group B streptococcus, and gram-negative organisms cause acute endocarditis.

S. aureus causes 80% to 90% of staphylococcal IE and is the most common cause of acute IE. Recent data from the International Collaboration on Endocarditis (ICE) suggest that *S. aureus* has become the leading cause of IE worldwide in injection drug users and prosthetic valves and most often presents as an acute disease.

Strep accounts for 60–80% of all endocarditis cases. Viridans streptococci are responsible for 30–65% of native valve endocarditis in adults. *S. bovis* is often associated with a GI malignancy in the elderly as well as polyps and diverticulosis—order colonoscopy in all patients with *S. bovis* endocarditis.

Enterococcal endocarditis is found in older men with genitourinary disease or after instrumentation or surgery.

S. aureus (coagulase-positive), *S. epidermidis* (coagulase-negative), and gram-negative endocarditis are seen in IV drug abusers and patients with prosthetic heart valves. Other risk factors for these types of IE include dialysis, Type I diabetes, burn victims, HIV, certain chronic dermatologic conditions, and patients with recent surgical incisions (including median sternotomy for valve replacement).

Right-sided endocarditis and the resulting septic pulmonary emboli can show up as RV enlargement and multiple lung infiltrates on chest x-ray. Onset of heart failure is a bad sign. When there is right-sided endocarditis, it

QuickQuiz

- What are the procedures of choice for diagnosing a dissecting aortic aneurysm?
- At what size is surgery indicated for a thoracic aortic aneurysm?
- At what size is surgery indicated for an abdominal aortic aneurysm?
- Which *Streptococcus*, if found as a cause of endocarditis, warrants a colonoscopy?
- Which type of ASD requires antibiotic prophylaxis before a dental procedure? Which of these require antibiotic prophylaxis: Previous CABG? VSD? Mitral valve prolapse without murmur? Mitral valve prolapse with murmur? Prosthetic valve? Are your answers based on the ACC/AHA 2008 guideline update?

is almost always due to IV drug abuse; however, IVDA-associated left-sided endocarditis occurs even more commonly! (Left-sided endocarditis has a higher incidence, and it has many more causes.)

Occasionally, endocarditis presents only with signs of embolic events, such as black toes or septic emboli to other organs. It may also present as an illness of smoldering, nonspecific symptoms (weight loss, fevers, chills, night sweats, etc.) or heart failure due to valvular insufficiency.

Classic physical exam findings include new regurgitant heart murmurs, Osler nodes (tender nodules on the pads of the digits), Janeway lesions (nontender macules on the palms and soles), splinter hemorrhages (Image 5-8), and Roth spots.

Blood cultures are positive in right- and left-sided endocarditis with equal frequency (95%). This is because there is a constant level of bacteremia in endocarditis; whereas with most other bacterial causes of fever, the bacteremia precedes the temperature spike.

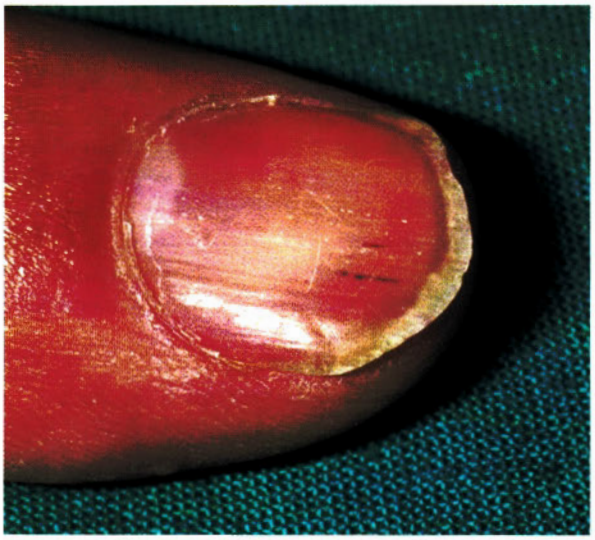


Image 5-8: Splinter hemorrhage on fingernail in endocarditis

Diagnosis of endocarditis is by the Duke Criteria; echo, including TEE, is frequently used to help make the diagnosis. Diagnosis is covered in the Infectious Disease section, Book 1.

Endocarditis occurring within 2 months of prosthetic valve placement means the valve was seeded when the valve was implanted. It is harder to treat (especially if *S. epidermidis*); if there is no response to one round of adequate antibiotics, replace the valve.

If it has been > 2 months since the prosthetic valve placement, antibiotic treatment is usually sufficient. The valve must also be replaced if there is evidence of valve ring infection or myocardial penetration or unstable prosthesis. These may show up as a new heart block or a new BBB.

Surgery is indicated in endocarditis for refractory heart failure usually from acute valve regurgitation, extension of the infection to the myocardium (or perivalvular abscess), failure of medical therapy, or large vegetations with systemic emboli or recurrent emboli on adequate therapy.

For treatment of infective endocarditis, see the Infectious Disease section, Book 1.

Antibiotic Prophylaxis

Overview

Know the following from the ACC/AHA 2008 focused Update on Infective Endocarditis.

Significant changes to the bacterial endocarditis prophylaxis prevention guidelines have been made because it has become clear that infective endocarditis is more likely to occur from bacteremia caused by brushing teeth than from medical procedures. It appears that medical procedures cause little if any infective endocarditis.

Indications for Prophylaxis

Prophylaxis is no longer indicated for GI/GU surgeries. Prophylaxis prior to dental procedures is now indicated only for patients with specific highest-risk-for-IE cardiac conditions:

- Prosthetic valves
- Previous episode of endocarditis
- Congenital heart disease (CHD)
  - Unrepaired cyanotic CHD
  - Repaired CHD within 6 months of procedure
  - Repaired CHD with residual defects
- Cardiac transplant patients with valve lesions

Prophylaxis is no longer indicated for bicuspid aortic valve, any ASD, VSD, native valvular stenosis or regurgitation, mitral valve prolapse (with or without murmur), CABG, or HCM (unless repair occurs within 6 months of procedure).

Table 5-6: Endocarditis Prophylaxis — Dental Procedures

Situation	Antibiotic	Regimen
Oral prophylaxis	Amoxicillin	2 gm orally
Unable to take oral medications	Ampicillin or Cefazolin* or Ceftriaxone	2 gm IM/IV 1 gm IM/IV
Allergic to penicillin	Clindamycin or Cephalexin* or Azithromycin or Clarithromycin	600 mg orally 2 gm orally 500 mg orally
Both allergic to penicillin and unable to take oral meds	Clindamycin or Cefazolin* or Ceftriaxone	600 mg IM 1 gm IM/IV

*Note: Cephalosporins should not be used if the PCN allergy is an immediate-type hypersensitivity reaction.
Note: Antibiotics (PO or parenteral) are given 30 to 60 minutes before the procedure.

Table 5-7: Modified Jones Criteria for the Diagnosis of Rheumatic Fever

Major	Minor
Carditis	Previous rheumatic fever
Polyarthritis	Arthralgias
Chorea	Fever
Erythema marginatum	Acute phase reactants (high sed rate or WBC)
Subcutaneous nodules	ECG changes: prolonged PR interval

To make the diagnosis: requires 2 major criteria or 1 major and 2 minor criteria AND evidence of a preceding group A strep infection (positive strep test or rising or elevated [> 250 Todd units] ASO titers).

Antibiotic Selection for Prophylaxis

Know the following:

Dental procedures: All dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa require prophylaxis in high-risk patients. See Table 5-6!

GU/GI procedures: Prophylaxis is not indicated in these high-risk patients for any GI or GU procedures.

Respiratory tract procedures, or skin, or musculoskeletal tissue infection: The high-risk patient should receive prophylaxis that covers staphylococci and beta-hemolytic streptococci.

RUBELLA

Rubella during pregnancy is a common cause of patent ductus arteriosus (PDA), supravalvular aortic stenosis, branch pulmonary artery stenosis ("peripheral PS"), and other congenital cardiac defects.

RHEUMATIC FEVER

Rheumatic fever is common outside of the U.S., with more than 470,000 cases worldwide. In the U.S., the latest incidence is about 2–14 cases/100,000. In patients with pharyngitis, always swab throats for a strep screen. Joint affliction in rheumatic fever is distinguished from rheumatoid arthritis by the lack of typical joint deformities and a negative rheumatoid factor. The associated carditis usually has no symptoms referable to the heart!

Rheumatic fever occurs more frequently in overcrowded areas. It is the most common cause of mitral stenosis and tricuspid stenosis (Table 5-7, diagnosis).

SPECIFIC VALVE LESIONS

Note

Refer to Table 5-8 and Table 5-9 on page 5-30 and page 5-31 as you study these valve lesions.

Aortic Stenosis

Aortic stenosis (AS) is generally due to age-related, calcific valve degeneration. Congenital bicuspid aortic valves usually start getting calcified and stenotic between ages 40 and 70 years, while the normal tricuspid aortic valves become stenotic at > 75 years old. A bicuspid aortic valve is the most common congenital valve disorder (1–2%). Less frequently, rheumatic heart disease may also cause AS, generally in the setting of mitral valve disease.

Presenting signs and symptoms include the classic triad of left ventricular failure, angina, and syncope with exercise.

Bedside physical exam with significant AS: The carotid pulse has a slowed upstroke and decreased amplitude (parvus et tardus), and the heart has a sustained apical impulse. Associated heart sounds include:

- A mid-to-late peaking, diamond-shaped systolic ejection murmur (SEM) at the right upper sternal border (RUSB) or suprasternal notch, which radiates to the neck
- An S_4 gallop
- Often a decreased or absent 2nd heart sound due to decreased mobility of the aortic valve leaflets
- A paradoxical S_2 split with severe AS

Occasionally, an AS murmur is transmitted to the apex, where it may be confused with the systolic murmur of mitral regurgitation (MR; Gallavardin effect).

Quick Quiz

- When should valve replacement occur for aortic valve stenosis?
- Name 4 conditions that cause chronic aortic regurgitation.

The systolic ejection murmur of AS is louder with squatting, whereas the murmur of hypertrophic obstructive cardiomyopathy (HOCM) decreases.

An ejection click sounds like a guitar string being plucked immediately after S_1. This ejection click is classic and common in bicuspid aortic valve patients but is not heard with age-related calcific AS. Ejection clicks may also be heard in patients with pulmonary artery stenosis.

With aortic stenosis, a systolic thrill can sometimes be felt over the upper precordium and the suprasternal notch. This thrill is a palpable sensation similar to feeling the purring of a cat.

Doppler echo is very accurate in detecting severe AS. A left heart cath is typically used in the determination of AS if there is a discrepancy between clinical and echo findings—or to detect concomitant coronary artery disease.

Patients with AS have a high rate of coronary artery disease (CAD): 1/3 in those 40–60 years of age and 2/3 in those > 60.

AS severity by valve area:

- Mild = 1.9–1.5 cm^2
- Moderate = 1.5–1 cm^2
- Severe = ≤ 1 cm^2

Mean gradients are also frequently used:

- Mild = < 25 mmHg
- Moderate = 25–40 mmHg
- Severe = >40 mmHg

Without surgical intervention, median survival depends on clinical presentation:

- Angina = 5 years
- Syncope = 3 years
- Heart failure = 2 years

Results with surgical treatment are much better, so order valve replacement early for all symptomatic patients. It is also indicated for patients with severe asymptomatic AS who develop LV dysfunction or who need CABG.

Percutaneous methods of valve replacement are currently under investigation for symptomatic patients who are high-risk surgical candidates.

Caution must be used with vasodilators in the treatment of ventricular failure due to AS. Aortic stenosis has the worst prognosis of all valvular lesions, and medical therapy alone is not effective.

Chronic Aortic Regurgitation

Chronic aortic regurgitation (AR) occurs as a result of valve deformity (e.g., bicuspid valve, rheumatic fever, endocarditis, or degenerative valve disease) or an abnormal aortic root (e.g., dilation seen in Marfan syndrome, senile aortic disease, giant cell arteritis, relapsing polychondritis, or syphilis).

Chronic AR causes LV volume overload, which eventually will cause LV dilation and a drop in LV systolic function.

Bedside physical exam with chronic AR: Chronic aortic regurgitation has several classic physical findings:

1) A decrescendo diastolic high-pitched blowing murmur caused by the regurgitation through the valve. This murmur is loudest at the **Left** sternal border (3rd space) if due to the aortic **Leaflet**, and at the **Right** sternal border (RSB) if due to aortic **Root** disease (because the root is closer to the RSB). The high-pitched blowing sound of this murmur indicates a high flow, whereas mitral stenosis, which also causes a diastolic murmur, causes a low-flow diastolic "rumble."
2) Occasionally, you hear an Austin Flint murmur, which does sound similar to the low-flow rumble of mitral stenosis. It is thought to be due to the high-pressure regurgitant jet striking the anterior mitral leaflet and impeding mitral valve inflow by causing early closure. This murmur is not associated with a presystolic accentuation as seen in MS.
3) A wide and bounding "Corrigan's" pulse 2° to elevated systolic and low diastolic components of BP that causes "water-hammer" arterial pulses.
4) There are many other exam findings associated with chronic AR that have eponyms and are all related to pulsations; e.g., Becker sign = visible pulsations of the retinal arteries; de Musset sign = bobbing of the head with the pulse.

Chest x-ray shows an enlarged left ventricle and may show dilation of the ascending aorta. Aortic angiography may be performed at the time of cardiac cath and is the gold standard to diagnose AR—although it is more frequently diagnosed with echo.

Patients with chronic AR should be monitored with echocardiograms to follow chamber size and LV function.

Treat chronic and severe AR with vasodilators. Routine use of vasodilator therapy is no longer recommended for non-severe AR. ACE inhibitors/ARBs are typically used, along with diuretics to treat symptoms. Valve surgery is indicated if the patient is symptomatic or when echocardiogram shows LV end-systolic dimension > 55 mm, LV end-diastolic dimension > 75 mm, or EF < 55%.

Table 5-8: Heart Defects and Associated Sounds (1 of 2)

Valve defect	Murmurs	Clicks	Change in Heart Sounds	Pulse Waveforms; *a*/*v* Waves
Aortic Stenosis	S: SEM at RUSB, mid-to-late peaking, diamond shaped	S: Ejection click if congenital or bicuspid	Absent S_2 (occ); S_4; Parodoxically split S_2	Slowed carotid upstroke
Mitral Stenosis	D: Diastolic rumble	D: Opening snap (only diastolic click!)	S_1 is enhanced, sometimes "snapping." May be silent if severely calcified	Large left *a* waves and *y* descent
Chronic Aortic Regurgitation	S: Occasional early systole SEM. D: 1) High pitched, decrescendo early to holodiastolic (regurgitation through the valve) 2) Austin Flint: low, rumbling diastolic (regurgitant stream striking the anterior mitral leaflets)		S_3 if severe	"Corrigan's pulse"; "Water-hammer pulse"
Acute Aortic Regurgitation	D: Short diastolic murmur		S_3 if severe	Thready
MVP with Murmur; Chronic Mitral Regurgitation (CMR)	S: MVP: Late SEM follows click. CMR: Pansystolic constant murmur	S: MVP: Mid-systolic click (Click-murmur syndrome)	S_3 if severe; S_4	
Acute Mitral Regurgitation	S: Pansystolic decrescendo at apex		S_3 if severe	Large left *v* waves
Pulmonic Stenosis		S: Ejection click	Persistently/widely split S_2	Large right (jugular) *a* wave
Tricuspid Stenosis	D: Diastolic at LSB			Giant right *a* waves
Tricuspid Regurgitation	D: Systolic at LLSB			Large right *v* waves
VSD	S: Holosystolic at LLSB			
ASD – Ostium Secundum	S: SEM at LSB (increased flow across pulmonic valve)		Fixed-split S_2	
ASD – Ostium Primum	S: SEM at LSB (increased flow across pulmonic valve); also often associated TR or MR murmur		Fixed-split S_2	
Coarctation of the Aorta	Midsystolic to continuous murmur (depending on severity) in the upper back			
HCM	S: Harsh midsystolic murmur		S_4	Brisk carotid upstroke that is BIFID in 2/3
PDA	S+D: Continuous "machinery" murmur at LUSB		Paradoxically split S_2	

*Squatting or lying down; or raising legs if already supine.

... Persistently/widely split S_2 (still varies with inspiration but never goes away) occurs with pulmonic stenosis, PE, RBBB, LV ectopic beats.

... Fixed split S_2 (A_2-P_2 interval remains the same throughout breathing cycle) from ASD.

... Paradoxically split S_2 (P_2 before A_2) is caused by severe HCM, LBBB, RV ectopic beats, AS, and PDA.

Table 5-9: Heart Defects and Associated Sounds (2 of 2)

Murmur Louder with:	CXR	Other:	Valve Defect
Squatting*, Expiration After PVCs	LVE	Sustained apical impulse; Etio: Bicuspid valve Classic triad is LVF, angina, and syncope with exercise	Aortic Stenosis
Squatting*, Expiration	LAE	Etio: Virtually always rheumatic fever SSx: Hemoptysis. Secondary pulmonary HTN	Mitral Stenosis
Squatting*, Expiration	LVE	Etio: Congenital, endocarditis, or dilated aortic root from: Marfan, VSD, arteritis, polychondritis, syphilis	Chronic Aortic Regurgitation
Squatting*, Expiration	Normal	Cardiogenic shock and pul edema Consider aortic dissection	Acute Aortic Regurgitation
Standing or Valsalva: Longer—moves earlier into systole; sustained handgrip. Expiration	LAE	Etio of MVP: Congenital; ischemia	MVP with Murmur; Chronic Mitral Regurgitation (CMR)
Squatting*, Expiration	Normal	Etio: Endocarditis, MI with papillary muscle ischemia or rupture, chordae tendineae rupture; SSx: Pul edema	Acute Mitral Regurgitation
Inspiration	RVH; enlarged pulmonary artery	Etio: Virtually always congenital—rarely caused by rheumatic fever and carcinoid; Congenital type usually does not progress	Pulmonic Stenosis
Squatting*, Inspiration	RAE	TS is rare; Etio: Usually rheumatic fever but also congenital and carcinoid synd. With carcinoid, pt. usually also has TR SSx: Venous congestion	Tricuspid Stenosis
Squatting*, Inspiration	RVE	Etio: Usually dilation from pul HTN; other: rheumatic fever, endocarditis (IVDA), carcinoid. Liver pulsations, JVD	Tricuspid Regurgitation
Handgrip	RVE + LVE	Consider in new MI with new systolic murmur	VSD
	RVE; shunt vascularity	ECG: RAD, RBBB	ASD – Ostium Secundum
	RVE	ECG: LAD, RBBB	ASD – Ostium Primum
	Rib notching, loss of aortic notch		Coarctation of the Aorta
Standing, Valsalva. Note: Sustained handgrip decreases murmur.	LVE	Apical impulse may have double- or triple-taps	HCM
	Calcification of ductus arteriosis		PDA

Note that S_4 is also heard in ischemic heart disease, diabetic cardiomyopathy, and hypertensive heart disease with concentric hypertrophy.

Note: RIght-sided murmurs sound louder on Inspiration; lEft on Expiration; Note: All right-sided valve problems can rarely be caused by carcinoid.

Cannon *a* waves occur in complete heart block and with ventricular pacing.

Intraaortic balloon pump placement is contraindicated in patients with aortic regurgitation.

Acute Aortic Regurgitation

Native acute AR is usually caused by a flail leaflet due to:

- endocarditis,
- type A aortic dissection, or
- trauma.

Prosthetic valve acute AR may be caused by:

- Tissue valve leaflet rupture
- Mechanical valve closure problem (e.g., thrombosis)
- Paravalvular regurgitation due to infection

Patients with acute AR present severe pulmonary edema and low cardiac output. Because the cardiac output and BP are low, there is no bounding arterial pulse. The diastolic murmur is short because it ends when the ventricular pressure rises to the level of the low aortic pressure. The LV in these patients does not have time to compensate for the LV volume overload.

Patients with significant acute AR and heart failure without a reversible cause almost always need immediate surgery.

Mitral Stenosis

Mitral stenosis (MS) is relatively rare in the U.S. It is almost always due to rheumatic fever. Other causes are SLE, rheumatoid arthritis (RA), and severe valve calcification. Atrial fibrillation is common. MS can cause CHF, but sometimes 2° pulmonary hypertension is the main physical finding.

Bedside physical exam with MS: Patients have a diastolic murmur with a diastolic opening snap. As mentioned in heart sounds, the S_1 is accentuated and may also have a snapping quality. The diastolic murmur is often described as a "rumble," which suggests low flow, in contrast to the high-pitched, high-flow diastolic murmur heard in aortic regurgitation.

The chest x-ray shows the following triad:

1) Prominent pulmonary artery revascularization
2) An enlarged left atrium (See straightening of left atrial border in Image 5-9.)
3) Normal-sized LV

The ECG also shows the enlarged left atrium. Do an echo to confirm the diagnosis. Hemoptysis may occur in patients with MS; it is due to rupture of the pulmonary bronchial vessels distended by pulmonary venous hypertension.

Pregnancy. The initial presentation of MS in a pregnant patient may be new-onset atrial fibrillation and pulmonary edema. The increased blood volume in pregnancy can cause a precipitous exacerbation of MS—so consider treating all pregnant MS patients with digoxin. Never

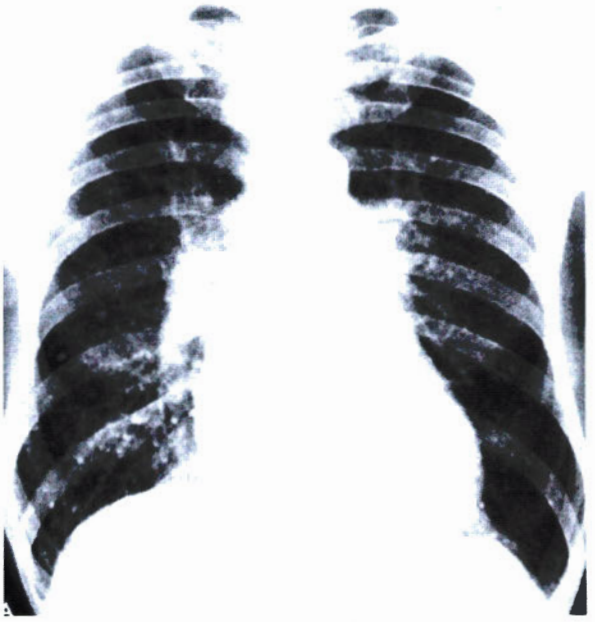


Image 5-9: Mitral stenosis with enlarged left atrium

give warfarin in the 1st trimester; it is teratogenic. To be safe, don't give it at all to pregnant patients. Give adjusted-dose heparin instead. Elective DC cardioversion, procainamide, digoxin, and verapamil are all okay during pregnancy.

All non-pregnant patients with MS-caused atrial fibrillation should be anticoagulated with warfarin.

Do percutaneous valvotomy in patients with symptomatic MS or asymptomatic MS with pulmonary hypertension (pulmonary artery systolic pressure > 50 mmHg at rest or > 60 mmHg with exercise). Surgical mitral valve replacement is less desirable but frequently is a necessary alternative, especially if severe calcification of the valve or significant mitral regurgitation is present.

Chronic Mitral Regurgitation

Chronic MR can be due to rheumatic heart disease, mitral valve prolapse (below), annulus dilation from left ventricular dilation, prior episode of endocarditis, and/or ischemic effects on the papillary muscle (from coronary artery disease or MI). Chronic MR presents differently from acute MR. Because the heart has an enlarged left atrium in the chronic form, there is less back pressure to the flow across the incompetent mitral valve, resulting in a constant intensity, holosystolic murmur instead of decrescendo (as in acute MR). Atrial fibrillation frequently develops. In both severe chronic and acute MR, the S_1 is soft or absent and S_2 is widely split. (The aortic valves close early because of decreased volume ejected from the left ventricle.) An S_3 is common in severe MR.

The left ventricular ejection fraction (LVEF) in MR is frequently normal or above normal, because LV outflow now has 2 routes of exit during systole (forward through the aorta and backward through the regurgitant mitral

QuickQuiz

- What is the usual treatment for acute aortic regurgitation?
- Which type of murmur occurs in mitral stenosis?
- Which mitral lesion is associated with hemoptysis?
- What should you consider in a pregnant woman with new onset of atrial fibrillation and pulmonary edema?
- Is elective electrocardioversion okay in pregnancy?
- Describe the murmur sometimes heard with MVP.
- Carcinoid usually results in what type of tricuspid murmur?

valve). Significant MR should be treated with diuretics and afterload reducing agents (ACE inhibitors/ARBs). Do surgery if the patient is symptomatic or if asymptomatic with:

- LVEF < 65%, and/or
- LV enlargement with left ventricular end-systolic diameter (LVESD) > 40 mm, or
- pulmonary hypertension.

Repair is preferable to replacement. Percutaneous valve repair is under investigation.

Mitral Valve Prolapse

Mitral valve prolapse is the most common valvular problem seen in practice (up to 2.4%) and is more common in women. There are different causes of MVP. Most MVPs are considered a normal variant; in these, the chordae tendineae are weakened, causing a billowing of the otherwise normal mitral valve leaflets. On the other hand, myxomatous changes in the mitral valve leaflets (determined by echo) invariably progress to mitral regurgitation. Many symptoms (dyspnea, panic attacks, chest pain, etc.), previously attributed to MVP, have been shown to occur with no greater frequency than in otherwise healthy people.

Bedside physical exam with MVP: These patients have a midsystolic click (followed by a mid-to-late systolic murmur [click-murmur syndrome] if there is associated MR). The murmur of MVP is like the murmur in hypertrophic cardiomyopathy (HCM) in that decreased preload increases the intensity of the murmur. The click and murmur become louder and move earlier into systole with standing or Valsalva, both of which decrease preload and hence, LV volume.

This gives the clue for how you can tell the difference between an ejection click (aortic or pulmonary stenosis) and the midsystolic click—an ejection click is fixed, whereas the midsystolic click varies in timing with changes in the patient's position. Stand the patient up, and the midsystolic click sounds just like an ejection click. Squatting or supine position increases LV size and causes the click to occur later, thereby shortening the murmur. Dynamic auscultation is required to diagnose MVP clinically.

Acute Mitral Regurgitation

Acute mitral regurgitation (AMR) usually presents with acute-onset pulmonary edema.

Native valve AMR causes:

- Flail leaflet (due to endocarditis, MVP, or trauma)
- Papillary muscle ischemia or rupture (MI, trauma)
- Chordae tendineae rupture (endocarditis, acute rheumatic fever, trauma, spontaneous)

Prosthetic valve AMR causes:

- Tissue valve leaflet rupture
- Mechanical valve closure problem (e.g., thrombosis)
- Paravalvular regurgitation due to infection

Bedside physical exam with AMR: Decrescendo systolic murmur at the apex. Echocardiogram shows a hyperactive LV with normal-to-high ejection fraction and a normal-sized left atrium. There are large, left-sided *v* waves on wedge pressure tracing.

Treat with afterload reduction and diurese. Unlike severe AR, intraaortic balloon pump (IABP) may be helpful for patients in heart failure from AMR. Urgent surgery is often required.

Tricuspid Stenosis

Tricuspid stenosis (TS) is rare. Causes are rheumatic fever (usual), congenital, carcinoid syndrome, and endocarditis. If the cause is carcinoid, the TS is generally found in association with tricuspid regurgitation (TR). Note: Carcinoid can affect either right-sided heart valve and typically implies a hepatic tumor if valvular involvement is present. (The pulmonary vascular bed is usually quite effective in removing the active 5-HIAA products that lead to valve damage.) Patients have systemic venous congestion without pulmonary venous congestion or pulmonary hypertension.

Bedside physical exam with TS: Patients have a diastolic murmur along the left sternal borders, which increases with inspiration (as do all right-sided murmurs). They have a giant *a* wave, caused by backflow during atrial contraction against a stenotic tricuspid valve. There may be ascites and lower-extremity edema.

The ECG shows the tall, peaked P waves in II and V1 (evidence of the right atrial hypertrophy) but no indications of right ventricular hypertrophy (RVH). Chest x-ray shows an enlarged right atrium.

Treat the underlying disease and perform surgery.

Tricuspid Regurgitation

Tricuspid regurgitation (TR) often is a functional result of RV dilation, which can be caused by end-stage left ventricular failure, submassive pulmonary embolism, or other causes of pulmonary hypertension. TR can also be caused by rheumatic heart disease, endocarditis, carcinoid, and congenital disease—Ebstein anomaly. Endocarditis affecting the tricuspid valve is usually seen in drug abusers, and it is often caused by staph; also consider *Candida*.

Bedside physical exam with TR: Patients have a holosystolic murmur along the lower left sternal border (increases with inspiration) that does not radiate to the axilla. Severe TR may cause a parasternal heave, liver pulsations, venous distention, ascites, and lower extremity edema (signs of RV failure). There are large, jugular *v* waves, reflecting the backflow through the tricuspid valve during ventricular contraction.

Diagnose with echo. Treat the underlying disease. Antibiotic treatment is usually sufficient for endocarditis; the valve rarely needs to be removed, unless the cause is *Candida*. Surgery also may be indicated in circumstances of severe destruction of the valve.

Pulmonic Stenosis

Pulmonic stenosis is virtually always congenital, and it typically does not progress! It is a fairly common congenital valve anomaly in adults. Rarely, it is caused by rheumatic heart disease or carcinoid. It may cause RV hypertrophy. Although it is usually not seen along with other abnormalities, it does occur in Noonan syndrome, in which the patient has low-set ears and hairline.

Bedside physical exam with severe pulmonic stenosis: Patients have an ejection click and a prominent jugular *a* wave, which is caused by backflow during atrial contraction against an inadequately emptied right ventricle.

If needed, open the stenotic pulmonic valve with balloon valvuloplasty.

Pulmonic Regurgitation

Pulmonic regurgitation is usually secondary to pulmonary hypertension (e.g., primary, cor pulmonale, mitral stenosis), but it may be due to a primary valve lesion (congenital, rheumatic heart disease, endocarditis, carcinoid). Pulmonary artery pressure is > 60 mmHg in patients with secondary pulmonic regurgitation.

Ebstein Anomaly

With Ebstein anomaly, the tricuspid septal leaflet is positioned lower in the ventricle than normal ("apically displaced")—so the RA appears huge and the RV small. Tricuspid regurgitation (TR) murmur is common. It is occasionally seen with atrial septal defect (ASD) and may cause WPW syndrome.

VALVE SURGERY

In general, valve surgery is indicated for any valve problem if the patient is symptomatic at rest or with low levels of exertion. Even though there is high mortality, valve surgery is better than no surgery in patients with severe valve disease and ventricular failure (since the natural history in these cases is 100% early mortality).

Porcine valves are less durable (especially in young patients and those on hemodialysis) but do not require anticoagulation. These are indicated in patients with a life expectancy of < 5–10 years and those with contraindications to anticoagulation (chronic bleeding problems, ulcers). They are also often given to women of childbearing age to avoid having to use anticoagulants during pregnancy.

Mechanical valves are used for all others and do require anticoagulation, but they are very durable typically lifelong in most cases.

Balloon valvuloplasty is the procedure of choice in pulmonic valve stenosis and frequently mitral stenosis —but not aortic stenosis due to a very high short-term restenosis rate (6–12 months).

For mitral regurgitation (MR), if surgery is required, do **valve reconstruction** whenever possible because it has better outcomes than MV replacement. Reconstruction is valve repair and/or annuloplasty with an annuloplasty ring and is especially likely to be done with MVP, ruptured chordae, flail leaflets, endocarditis, and annular dilation. Valve replacement is usually necessary in MR that is due to rheumatic fever.

The major determinants in prognosis after valve surgery include ejection fraction, degree of symptoms, and type of valve surgery (valve repair is better than replacement). Echocardiography is best for checking for prosthetic valvular function. A transesophageal echo (TEE) is especially useful for checking mitral valve prosthesis. Fluoroscopy is also a useful tool for documenting leaflet motion with mechanical valves if valve dysfunction is suspected.

When anticoagulating mechanical valves, keep the INR 2.0–3.0 for the aortic valve and 2.5–3.5 for the mitral valve. A mechanical mitral valve has a higher risk for a thrombus formation compared to an aortic (hence the higher INR requirement). Therefore, if holding warfarin for a procedure or surgery, then bridging anticoagulation with heparin is recommended for mechanical mitral valves.

Final Pearls about Murmurs

[Know:]

- Aortic stenosis: suprasternal notch thrill with systolic murmur, paradoxically split S_2
- Chronic aortic regurgitation: early diastolic, blowing, decrescendo murmur heard best at left sternal border, 3rd intercostal space, with patient leaning forward

QuickQuiz

- Ebstein anomaly is occasionally associated with which structural and electrical abnormalities?
- What are the major prognostic factors after valve surgery?
- Describe the abnormal heart sounds found in AS, Chronic AR, and MS.
- What are some of the tests used to work up syncope?

and exhaling; also, low-pitched late-diastolic rumble (Austin Flint)
- Mitral stenosis: hemoptysis, opening snap, low-pitched diastolic murmur at the apex

Valsalva (one last time): decreases the murmur of AS, increases the murmur of hypertrophic cardiomyopathy, and increases the murmur of mitral valve prolapse.

ARRHYTHMIAS

SYNCOPE DUE TO ARRHYTHMIAS

Syncope may be caused by arrhythmias. Do 24- to 48-hour ambulatory monitoring. Do CT and EEG if history suggests seizures or if neurologic deficits exist (usually not caused by arrhythmia).

VT brought on by exercise, as may occur during an exercise stress test, may be related to ischemia but also could be a non-lethal form of ventricular tachycardia called right-ventricular outflow tract VT (RVOT VT). RVOT VT can be treated with beta-blockers or calcium channel blockers as 1st line and then with radiofrequency ablation if medical treatment is not satisfactory.

Syncope not due to arrhythmias is discussed on page 5-42.

MECHANISMS OF ARRHYTHMIAS

The 3 usual mechanisms of abnormal rhythms are reentry, triggered, and automaticity. The reentrant mechanism is the cause of most abnormal rhythms, especially premature complexes, most SVTs, atrial flutter, and VT.

Atrioventricular (AV) nodal reentry causes 2/3 of reentrant tachycardias (previously PSVTs). Automatic rhythms are accelerated ectopic rhythms. RVOT VT (see above) is an example of a triggered rhythm; triggers can include exercise or other adrenergic stimuli. Parasystole is a 3rd mechanism that is another cause of PVCs. It is an automatic depolarization of an ectopic focus at a slow rate. This results in a variable coupling interval, fusion beats, and a regular interval between the PVCs. Do not treat parasystole. Be able to diagnose all rhythms at a glance (see ECG section, page 5-54).

SICK SINUS SYNDROME

Sick sinus syndrome causes any one (or combination) of sinoatrial node problems, including sinus bradycardia, sinus pauses/blocks/sinus arrest, and tachy-brady syndrome (profound bradycardia/sinus arrest upon reverting from atrial fib to sinus rhythm, for example). These patients usually do not need electrophysiologic testing. Because prognosis is good, there are only 2 indications for treatment with a pacemaker:

1) Symptomatic patient
2) Patient with tachyarrhythmias or other conditions requiring therapy that might precipitate significant bradycardia (beta-blockers for CAD, for example)

HEART BLOCK

Permanent pacing is indicated if there is a Mobitz II or complete heart block—especially if symptomatic. See Arrhythmias and Blocks, starting on page 5-20, for more detailed pacing criteria post-MI.

To differentiate between AV node block vs. infranodal block: AV node block has narrow complexes, has escape focus rate > 40 bpm (typically 40–60 bpm), and is responsive to atropine.

SUPRAVENTRICULAR TACHYCARDIAS

Atrial Flutter

Type I atrial flutter, the common form, has a characteristic atrial rate of 300 bpm (240–340)—commonly with a 2:1 AV block. It can be counterclockwise, characterized by negative sawtooth flutter waves or clockwise, characterized by positive flutter waves in ECG leads II, III, and aVF. These two atrial flutter types share the same right atrial reentrant circuit around the cavo-tricuspid isthmus (circuit around the vena cavae and the tricuspid valve).

Atrial flutter is typically an indication of disease, most often either organic heart disease or pulmonary disease. Flutter is a relatively unstable rhythm and often spontaneously converts to either atrial fibrillation or a normal sinus rhythm.

The normal AV block is 2:1 with a ventricular rate of half the atrial rate. If it is ≥ 3:1, the cause is either AV node disease or drugs. Systemic embolization (most notably TIA/stroke) may occur but is less common in atrial flutter than in atrial fibrillation.

There is also a Type II atrial flutter with a much higher atrial rate: 340–440 bpm.

Vagal maneuvers or adenosine slow the ventricular rate and allow better diagnosis. Rule out pulmonary emboli (often multiple) and thyroid disease—especially if there is no heart or lung history.

The most effective treatment for atrial flutter is DC (direct current) cardioversion. Low energy (10–50 joules) can be used because it is an unstable rhythm to begin with. Even so, higher energy (100–200 joules) is often used because it is less likely than low-energy cardioversion to convert the rhythm to atrial fibrillation. Always shock if the patient is hemodynamically compromised.

Do not continue DC cardioversion if the patient repeatedly reverts back to atrial flutter.

Antiarrhythmic drugs can be used for nonemergent cardioversion. IV ibutilide is most effective and 1st line drug treatment for atrial flutter; however, be aware that it may cause QT prolongation (8%) and *torsades de pointes*.

Quinidine, procainamide, disopyramide, flecainide, and propafenone are effective. However, these drugs increase AV nodal conduction, so be sure to pretreat with verapamil, diltiazem, beta-blocker, or digoxin (particularly digoxin with heart failure or hypotension) to ameliorate conduction. See Antiarrhythmic Therapy on page 5-40.

In patients with atrial flutter and preexcitation syndrome (WPW), avoid digoxin, calcium channel blockers, and beta-blockers. See WPW, page 5-38.

Radiofrequency ablation is a treatment modality that can cure the most common types of atrial flutter (success rate 85–95%), and it is used for persistent or recurrent atrial flutter, although recent studies have suggested it is a reasonable 1st line approach in some circumstances.

Anticoagulate patients with chronic atrial flutter, as you would for atrial fibrillation (see next).

Atrial Fibrillation

Overview

Atrial fibrillation (A. fib) usually has a ventricular rate of ~ 150 bpm (130–200). This is about the same as the ventricular rate of atrial flutter with a 2:1 AV block.

A. fib is classified into 3 categories: paroxysmal, persistent, and permanent. Complications are embolic events—mainly stroke, and tachycardia-induced cardiomyopathy.

The most common clinical diagnoses associated with A. fib are hypertension and coronary artery disease (CAD). If the patient is > 40 years of age, screen for heart disease (echo, stress test) to rule out large left atrium, cardiomyopathy, hypertrophic cardiomyopathy, and CAD. A. fib is common in patients with COPD and hypoxemia due to right atrial dilatation.

With new-onset A. fib, or in A. fib not responsive to the usual treatment, consider hyperthyroidism, untreated or undertreated obstructive sleep apnea, hypomagnesemia, alcoholism/cocaine abuse, excessive caffeine, and nicotine as possible causes.

Treatment of A. Fib

Rhythm Control vs. Rate Control

You have 2 choices for the treatment of A. fib:

1) Rhythm control with conversion to a normal sinus rhythm
2) Rate control (no conversion), which decreases AV node conduction and hence ventricular rate so each ventricular contraction is effective

There are no differences in mortality between the 2 treatments. Rhythm control is usually attempted first—and DC cardioversion of A. fib is definitely indicated when the patient becomes very unstable or is crashing.

Rhythm Control: DC vs. Pharmacologic Cardioversion

You have 2 methods for cardioversion of A. fib:

1) Direct current (DC)
2) Pharmacologic

DC cardioversion is done with an R-wave synchronized DC pulse.

DC Cardioversion

In most cases, you have the option of doing electrical or pharmacologic cardioversion. It is often based on patient's preference.

Even so, DC conversion is generally preferred over pharmacologic conversion in stable patients with poor cardiac function (EF < 40%).

The exception is when it has been < 48 hours since onset of A. fib in the patient with poor cardiac function; in this case, amiodarone can be used rather than DC cardioversion.

Immediate DC cardioversion is required for:

- A. fib with rapid response that does not respond to medical therapy and there is evidence of ischemia, hypotension, angina, or heart failure
- Preexcitation with rapid tachycardia or hemodynamically unstable

Important points regarding DC cardioversion:

- With slow A. fib, consider inserting a temporary pacemaker before DC cardioversion because the patient probably has nodal disease and may have asystole after cardioversion.
- TEE-guided cardioversion is done frequently, especially if the time of onset of the A. fib is unclear. It is fast and cost-effective.
- Just like with atrial flutter, do not continue DC cardioversion if the patient repeatedly goes right back into A. fib shortly after being shocked.

Quick Quiz

- What is the treatment sequence for atrial flutter?
- In what circumstance is immediate DC cardioversion indicated for atrial fibrillation?
- What can happen after DC cardioversion to the patient who has A. fib with a slow rate? What intervention prevents this complication?
- According to current guidelines, what HR is an acceptable target for patients with A. fib?

Note: In what other scenarios do you not shock a patient with an abnormal rhythm (but stable hemodynamically)? Digitalis intoxication and hypokalemia.

Pharmacologic Cardioversion

When attempting pharmacologic cardioversion, use these guidelines—again, use is based on duration of symptoms:

- For A. fib > 7 days:
  - 1st line: dofetilide
  - 2nd line: amiodarone or ibutilide
- For A. fib < 7 days:
  - 1st line: dofetilide, flecainide, ibutilide, or propafenone (previously, dronedarone*)
  - 2nd line: amiodarone (Exception: If < 48 hours and poor cardiac function, amiodarone is 1st line.)

*July 2011—Dronedarone appears to cause a 2x increase in mortality in patients with permanent A. fib and class III and IV heart failure. Current recommendation is to not prescribe dronedarone to patients with permanent A. fib. Its position is also being reevaluated as treatment for periodic A. fib.

Maintenance Drugs for Rhythm Control

Which drugs are used to maintain sinus rhythm in those with recurrent/persistent atrial fibrillation?

This decision is based on underlying heart disease:

- No or minimal heart disease: flecainide, propafenone, or sotalol (dronedarone—see above). If ineffective, then amiodarone, dofetilide, or catheter ablation.
- Heart failure or EF < 35%: amiodarone or dofetilide (definitely not dronedarone!). If ineffective, then catheter ablation.
- Coronary artery disease: dofetilide or sotalol. If ineffective, then amiodarone or catheter ablation.
- Hypertension:
  - LVH present: Use amiodarone. If ineffective, then catheter ablation.
  - LVH not present: Use flecainide, propafenone, or sotalol. If these fail, then go to amiodarone, dofetilide, or catheter ablation.

Rate Control

2011 update says resting heart rate < 110 bpm is acceptable and is as good as strict control.

Beta-blockers (atenolol, metoprolol) or calcium channel blockers (diltiazem or verapamil) for rate control at rest and with exercise.

Digoxin is useful in A. fib with heart failure. Digoxin is not used as first-line agent and definitely not useful for controlling rate during exercise or exertion.

Radiofrequency ablation of the AV node with subsequent permanent pacing is a treatment for patients with refractory A. fib and for those who cannot tolerate the meds needed for rhythm control. This strategy provides definitive rate control but does not cure the underlying atrial fibrillation—hence, patients still require anticoagulation.

In many patients, A. fib originates as abnormal impulses arising in the pulmonary veins. Radiofrequency ablation, or isolation of the pulmonary veins, is becoming increasingly popular in treating recurrent A. fib, although it is not yet established as 1st line therapy.

Anticoagulation for A. Fib

Before and After Cardioversion

If it has been < 48 hours since the onset of A. fib, you can cardiovert most patients without any anticoagulation.

If it has been > 48 hours since the onset of A. fib and the patient is stable, you must achieve adequate anticoagulation before you attempt cardioversion. This is true even for stable patients with poor cardiac function (EF < 40%).

Achieve adequate anticoagulation in 2 ways:

1) Anticoagulate x 3 weeks; then cardiovert, followed by 4 weeks more of anticoagulation. Note: Anticoagulation can be accomplished via warfarin (INR 2–3) or with a newer direct thrombin inhibitor (dabigatran).
2) Start IV heparin (or LMWH, if appropriate); perform TEE, cardiovert within 24 hours, and then anticoagulate for 4 more weeks.

Chronic Anticoagulation

In this case, you are unable to convert the A. fib or the patient is being rate controlled. These patients must be on lifelong anticoagulation. The medications used are based on the CHADS2 scoring system:

- CHF (any history): 1 point
- HTN (prior history): 1 point
- Age ≥ 75: 1 point
- DM: 1 point
- Prior stroke, TIA, or embolic event: 2 points

Meds based on CHADS2:

- 0 points = ASA alone
- 1 point = either warfarin/dabigatran or ASA
- 2 points or more = warfarin/dabigatran

Dabigatran (Pradaxa®) is an oral anticoagulant that is a direct thrombin inhibitor and does not require an INR. There is no way to reverse the effect if a major bleed occurs. Dabigatran (2011 A. fib update) is useful as an alternative to warfarin and is recommended by many over warfarin (but do not use dabigatran in patients with renal insufficiency).

MAT

Multifocal atrial tachycardia (MAT) is usually diagnosed by ECG criteria of atrial rate > 100 beats/minute with P waves of at least three distinct morphologies.

MAT is usually seen in patients with pulmonary disease and may be a result of theophylline use. MAT can also be caused by very low K^+ and Mg^{+2}.

If the theophylline cannot be stopped, diltiazem and verapamil are effective suppressive treatments. Digoxin is of no use in MAT! It can actually worsen it, in addition to causing digoxin-toxic arrhythmias. You can use AV node ablation with permanent pacing for refractory cases.

PSVT

Paroxysmal supraventricular tachycardia (PSVT = PAT = reentrant tachycardia). Most are due to a reentrant rhythm, AV nodal reentrant tachycardia (AVNRT). Rate is 150–230 (same or slightly faster than A. fib or flutter). Usually, the P wave is not visible (buried in the QRS), but occasionally it is slightly anterograde or retrograde.

If the monitor shows narrow complexes, treat with vagal maneuvers, adenosine, or verapamil. Adenosine (Adenocard®) is the drug of choice because of its effectiveness and very short half-life (~ 10 seconds). It works primarily on the AV node where most of the SVTs originate, but it can suppress sinus node function as well. Most other antiarrhythmic drugs also are effective, especially Ia agents. Flecainide (Ic) is now approved for SVT, but most doctors try something else first.

Radiofrequency ablation can cure many types of PSVT. Differential diagnosis of wide-complex tachycardia includes PSVT with aberrant conduction, WPW, SVT with LBBB, and VT (see below). PSVT is associated with ASDs and Ebstein anomaly of the tricuspid valve.

WPW

Wolff-Parkinson-White (WPW; preexcitation syndrome): PR interval is < 0.12 seconds due to a delta wave. Total QRS is > 0.12 seconds because of the fusion between the impulse that uses the normal conduction system and that which uses the abnormal (accessory) pathway, which bypasses the AV node. This bypass tract (Kent bundle) conducts faster than the AV node; therefore, a portion of the electrical current reaches the ventricle sooner (the delta wave on the ECG) and preexcites the ventricle—hence the alternative name, "preexcitation syndrome." Occasionally, the accessory pathway is concealed, and the delta wave will not be visible. An unusual cause of WPW is Ebstein anomaly of the tricuspid valve.

Treatment of WPW: Most patients have completely asymptomatic WPW and no dysrhythmias. Patients with WPW and a narrow complex tachycardia (rate is usually ~ 190 bpm) can be treated with vagal maneuvers, cardioversion, procainamide, verapamil, or adenosine—same as any SVT! (In these cases, the impulses are moving down the normal conduction system and returning via the accessory pathway to complete the circuit.) But never treat acute A. fib or flutter (usually has a wide QRS) in WPW with digoxin, verapamil, or beta-blockers. Although verapamil and digoxin increase the refractory period in the AV node, they can preferentially enhance conduction down the accessory pathway and precipitate ventricular fibrillation.

Instead, treat acute A. fib or flutter in WPW with IV procainamide. Shock if there are any signs of hemodynamic deterioration in any WPW tachyarrhythmia; especially watch those with ventricular rate > 285 bpm because they are at greatest risk of V-fib.

WPW may be cured with radiofrequency ablation!

Note: DC cardioversion of SVTs: Most can be terminated with low energy: 25–50 joules. The exception is A. fib, which usually requires > 100 joules.

VENTRICULAR ARRHYTHMIAS

PVCs

Premature ventricular contractions (PVCs) often have a compensatory pause; that is, they do not reset the sinoatrial node; i.e., the time between the sinus beats that are on either side of the PVC = 2 basic RR intervals.

Asymptomatic, simple PVCs do not need to be treated if LV function is normal (even if the patient has thousands each day). If you do attempt treatment with antiarrhythmics (beta-blockers are 1st line), the PVCs should decrease by 80% for the treatment to be considered successful—otherwise, stop treatment. (Most patients have spontaneous resolution or decrease anyway.) Simple PVCs occur beyond the T wave, are uniform, and have constant coupling (reentrant).

Complex PVCs (pairs, triplets) also do not need to be treated if the patient is asymptomatic and has no heart disease!

Otherwise, base the treatment on electrophysiologic testing—this is especially helpful if the patient has a history of cardiac arrest not associated with an MI! If a patient

Quick Quiz

- In what patient group is MAT found?
- What is the treatment for A. fib or flutter in WPW?
- List the 7 ECG changes consistent with VT.
- With what type of tachycardia should you never use verapamil?

has had an MI and has an ejection fraction of < 40%, frequent PVCs (> 10/hour) indicate a high risk of sudden cardiac death—especially if they are sequential.

Ventricular Tachycardia

ECG Findings

Ventricular tachycardia (VT) is defined as ≥ 3 sequential PVCs, occurring at a regular rate of 100 bpm or faster. Most occur at a rate of 150–200 bpm. Differential diagnosis includes SVT with aberrant conduction, WPW, SVT with LBBB, and severe hyperkalemia causing very large, peaked T waves. VT is more likely if there is a previous history of angina or MI.

7 ECG changes indicative of VT [Know!]:

1) Severe left axis deviation. (Most VT is more negative than −30°, "northwest axis.")
2) QRS width of > 0.14 sec with a RBBB or > 0.16 sec with a LBBB. In SVT with aberrancy, the width is usually < 0.12 sec.
3) AV dissociation showing dissociated P waves. (So, the patient may have cannon *a* waves and variable heart sounds.)
4) QR or QS in V6 with a LBBB or a right axis deviation with a LBBB.
5) Fusion beat (looks like a "fusion" between a normal QRS and a ventricular beat).
6) A rate of > 100 bpm.
7) Capture beats.

VT may also be bidirectional, with the complexes alternating in direction; this is usually due to digitalis intoxication but may also be seen post-MI and in a relatively rare genetic condition called catecholaminergic polymorphic ventricular tachycardia (CPVT).

Differentiating PSVT with wide complexes vs. VT (in addition to the Brugada criteria): A RBBB (rSR' or rR' in V1) is seen more often in PSVT with aberrant conduction, while an RSr' or Rr' in V1 is more suggestive of VT.

If the VT lasts > 30 seconds or is unstable, it is usually due to organic heart disease. These patients have a high risk of sudden death, and, because of this danger, any patient with a wide QRS tachycardia and hemodynamic deterioration should have immediate electrocardioversion (treated like V-fib).

Treatment

For sustained monomorphic VT, do the following:

- Stable: Give IV amiodarone.
- Hemodynamically compromised: Shock.
- Unstable and refractory to electrical cardioversion: Give IV amiodarone/procainamide.
- VT specifically with acute MI: Most use amiodarone first. IV lidocaine is still listed in some older guidelines but is not used much.

For sustained polymorphic VT, do the same as monomorphic, except:

- IV beta-blockers if ischemia is suspected or cannot be excluded.
- IV amiodarone, as long as there is no prolonged QT.
- Urgent cath if ischemia is suspected.
- Assess for *torsades de pointes* (see below).

Do not ever use verapamil with any wide-complex tachycardias in the emergency setting. (30% of those with ventricular tachycardia will rapidly deteriorate!) VT that is consistently induced by exercise (RVOT VT) is well controlled by beta-blockers. Other VTs may require electrophysiologic testing. V. flutter appears as a sine wave at 150–300 bpm.

Implantable Cardioverter-Defibrillators (ICDs)

Implantable cardioverter-defibrillators (ICDs) are great! 5% mortality vs. 30% otherwise. The only problem is that, on rare occasions, they go off at the wrong time!

Use of ICDs for secondary prevention:

- VT and structural heart disease (especially HCM)
- VT and uncorrectable coronary artery disease
- VT in ischemic cardiomyopathy and EF < 35%
- VT in nonischemic cardiomyopathy, EF of < 35%, and NYHA class II–III heart failure symptoms

Use of ICDs for primary prevention:

- Patients with history of MI or CHF with an EF < 30% (MADIT II trial)
- Nonischemic cardiomyopathy with LVEF ≤ 35% (SCD-HeFT trial)

Torsades de Pointes

Torsades de pointes (TdP; [Know this topic!]) is a common type of polymorphic VT. It is usually preceded by a prolonged QT interval (> 500 ms) and a U wave (sometimes).

Drugs that commonly cause TdP are:

- Class Ia antiarrhythmics drugs (quinidine, procainamide, disopyramide)
- Class III antiarrhythmics (amiodarone, sotalol, dofetilide, and dronedarone)
- Tricyclics

You may also see it in association with very low K^+ or Mg^{+2} (as in MAT). Bradycardia can contribute to TdP as well.

Treat *torsades de pointes* with:

- Isoproterenol to increase the atrial rate.
- Overdrive pacing.
- Mg^{+2} sulfate—Give this if the patient has contraindications to the previous 2 options; i.e., with acute MI or severe ischemic heart disease.
- Shock, only as a last resort.
- Never treat with Class Ia or Class III AADs.

Nonsustained Ventricular Tachycardia

Nonsustained ventricular tachycardia (NSVT) is defined as VT (> 3 sequential PVCs with HR > 100 bpm) lasting for < 30 seconds.

NSVT typically indicates increased risk for death in patients with heart disease. NSVT patients are at risk of sustained VT and sudden death when:

- they have ischemic cardiomyopathy (LVEF < 40%), or
- sustained VT can be induced at electrophysiologic testing (EPT).

These patients benefit from ICD implantation.

Young, healthy patients with NSVT have a slightly increased risk for later heart disease. In these patients, rule out heart disease such as HCM. If there is none, they can be reassured and scheduled for long-term follow-up.

PACEMAKERS

For temporary pacing, dual-chamber (atrium and ventricle) pacing is best. A sinus heart rate of 40 bpm has same output as a single-chamber paced ventricular rate of 70 bpm.

For permanent pacing, there was no difference in all endpoints tested for 3 years between single chamber and dual chamber pacemakers. These included mortality, A. fib, heart failure, or findings of stroke/TIA/thromboembolism.

Use permanent pacing for symptomatic sinus bradycardia and complete heart block. Also, patients who have a Mobitz II heart block after an anterior MI survive longer with permanent pacing—see Arrhythmias and Blocks on page 5-20.

The most common pacemaker (Table 5-10) is DDD, which stands for Dual-chamber paced, Dual-chamber sensed, and Dual response to sensing: triggered and inhibited. Most clinicians use DDD, unless the patient is in chronic, slow atrial fibrillation. The DDD is the most physiologic and provides better exercise tolerance.

"Pacemaker syndrome" (associated lightheadedness and/or syncope) may occur with single-chamber ventricular pacing and is usually cured by dual-chamber (DDD) pacers, which restore the atrial "kick."

"Pacemaker-mediated tachycardia" can occur when paced ventricular complexes are sensed by the atrial lead and then trigger subsequent ventricular paced beats; this cycle can continue indefinitely.

ANTIARRHYTHMIC THERAPY

Drugs

Overview

With antiarrhythmic drugs (AADs), always wait 4–5 half-lives before determining whether a drug is effective.

Notes:

- All AADs have a proarrhythmic potential.
- Per the CAST study, there is evidence that Ic antiarrhythmic drugs decrease survival in patients with ventricular arrhythmias that occur post-MI. The only drug that did show a benefit was a beta-blocker after a Q wave (ST-elevation) infarction.
- Mexiletine is effective in most patients who respond to lidocaine.
- Digoxin works by inhibiting membrane ATPase. It increases contractility and slows AV conduction and HR.
- Quinidine increases digitalis levels.

Class I: Sodium channel blockers which slow electrical conduction in the heart.

Ia: **Quinidine**, **procainamide**, **disopyramide**—slows conduction velocity and prolongs action potential duration.

Table 5-10: Permanent Pacemakers

Classification of Permanent Pacemakers: Breakdown of Their 3–4 Letter Code
First letter = Chamber Paced – V/A/D (Ventricle, Atrium, or Dual)
Second letter = Chamber Sensed – V/A/D/O (Ventricle, Atrium, Dual, or nOne)
Third letter = Mode of response – T/I/D/O (Triggered, Inhibited, Dual (T+I), or nOne)
Fourth letter = P/R – indicates whether Programmable or Rate-modulated (most are rate-modulated)

Quick Quiz

- Which antiarrhythmic drugs prolong the QT interval?
- What is the treatment for *torsades de pointes*?
- How long do you have to wait for an antiarrhythmic to reach steady-state therapeutic levels?
- When is it okay to use verapamil; when is it not okay?
- Which antiarrhythmic drug can cause lupus?

Ib: **Lidocaine**, **tocainide**, **mexiletine**, **phenytoin**—shortens action potential duration slightly.

Ic: **Flecainide** and **propafenone**—slows conduction velocity without effect on potential duration.

Class II: Beta-blockers—decrease heart rate and blood pressure by blocking impulses that may cause irregular heart rhythm and decreasing hormonal effects (e.g., adrenaline) on the heart.

Class III: Amiodarone, **sotalol**, and the newer agents, **dofetilide** (oral Tikosyn®) and **dronedarone** (Multaq®)—prolong the action potential by potassium channel blockade. Note: see side effects on dronedarone, below.

Class IV: Calcium channel blockers, especially verapamil and diltiazem—slow inward current. They decrease heart rate and blood pressure like class II.

Adenosine and Digoxin

Digoxin: Digoxin is not in the above classes of antiarrhythmics but it has antiarrhythmic effects and occasionally is used for this. Remember that digoxin is usually reserved for treating severe heart failure. It is only used in restrictive cardiomyopathy as an antiarrhythmic—for treatment of associated A. fib.

Adenosine is also not in the above groups. Adenosine slows conduction in the AV node and is used for conversion of SVT (AV node reentry) to normal sinus rhythm. It also induces coronary artery vasodilation and is used in cardiac perfusion imaging. It depresses LV function, but it has such a short half-life, it can even be used in patients with decreased LV function.

Notes on Verapamil

Avoid verapamil with:

- Atrial fibrillation or atrial flutter occurring in WPW
- Wide-complex tachycardias
- Beta-blockers—relative contraindication because they are both negative chronotropes and negative inotropes
- Patients with asymptomatic HCM
- Patients with obstructive HCM in the setting of systemic hypotension or severe dyspnea at rest

Okay to use verapamil:

- To control the ventricular response to A. fib or atrial flutter in an otherwise healthy heart
- MAT
- PSVT (2nd choice after adenosine)
- WPW with narrow complex tachycardia
- Symptomatic treatment in HCM (but look above regarding avoiding verapamil in HCM. See page 5-42.)
- Severe, concentric LVH
- Hypertension

Major Side Effects of AADs

[Know!] All AADs are, by their nature, arrhythmogenic. Especially remember the following:

Class Ia:

- **Quinidine**: prolongs the QRS complex and the QT interval—occasionally leading to *torsades de pointes*, diarrhea, and (rarely) autoimmune thrombocytopenic purpura. Also "cinchonism": hearing loss, tinnitus, and psychosis.
- **Procainamide**: Prolongs QT and QRS but also causes blood dyscrasias, such as agranulocytosis, neutropenia, and thrombocytopenia, in ~ 0.5%. It also causes drug-induced lupus and must be used with caution in HF patients because it has a mild myocardial depressive effect.
- **Disopyramide**: prolonged QT, QRS, and *torsades de pointes*. It is also anticholinergic and vagolytic, so it causes urinary retention, constipation, dry mouth, and negative inotropic effects. Because quinidine and disopyramide prolong both the QRS and QT intervals, avoid them in patients with 2nd or 3rd degree heart block. Disopyramide has a negative inotropic effect, so avoid in patients with HF.

Class Ib:

- **Lidocaine**: seizures.
- **Tocainide** is now used less often because of an association with aplastic anemia.

Class II: **Beta-blockers** commonly cause decreased libido and impotence. They must be tapered slowly.

Class III: All of them can cause prolonged QT, QRS, and *torsades de pointes*.

- **Amiodarone** is the most effective, but also, due to the extremely high iodine content, it is the most toxic antiarrhythmic drug. It causes corneal deposits in 98% of patients!—also, hyper/hypothyroidism, pulmonary fibrosis, gray skin, and sun sensitivity but not hematologic changes.
  Pulmonary fibrosis from amiodarone can be severe and is fatal 10% of the time. It usually occurs in the first year of treatment. It tends to occur only in older patients (> 40 years old), and in those with low CO

diffusing capacity. (Pulmonary fibrosis is unlikely to develop on a maintenance dosage of < 200 mg/day.) Amiodarone also causes a less common acute form of pulmonary toxicity.
Again, amiodarone: hepatic toxicity; extremely long half-life (40–55 days); hyper/hypothyroidism; gray skin.

- **Dronedarone**: July 2011—Dronedarone showed 2x increased mortality in patients with permanent A. fib and class III and IV heart failure. Current recommendation is to not prescribe dronedarone to patients with permanent A. fib. Its position is being reevaluated as treatment for periodic A. fib also.

Digitalis toxicity is more likely in elderly patients and in those with low K^+, low Mg^{+2}, or low pO_2 (low, low, low) and impaired renal function. The toxic levels of digoxin are determined by changes in the ECG, not by blood levels. Most common ECG changes are bradycardia and prolonged PR interval.

Electrophysiologic Testing

EP studies are most commonly used to identify and characterize SVTs and VTs, often as a precursor to radiofrequency ablation.

Radiofrequency Ablation

Radiofrequency ablation is the treatment of choice for WPW and for variant preexcitation syndromes.

It is also used for the following if the patient prefers it to standard drug therapy or the condition is not responsive to meds:

- PSVT (Atrial nodal and unifocal tachycardias and AV nodal reentrant tachycardia)
- Atrial flutter
- Idiopathic VT
- Other reentrant tachycardias

It has also been used to treat atrial fibrillation by ablating a focal source of A-fib or by destroying the AV node and placing a ventricular pacemaker.

SYNCOPE

Syncope has 3 causes. It can be neurally mediated (vasovagal), or caused by orthostatic hypotension or cardiac arrhythmias.

Don't forget that syncope with exercise is a common presentation for symptomatic AS as well.

Neurally mediated vasovagal syncope is the most common type of syncope in young, otherwise healthy people but also is common in older patients. Vasovagal syncope, as in the common faint, is triggered by intense emotion, pain, prolonged standing, alcohol, or heat exposure, whereas the situational reflex syncopes are triggered by cough, micturition, etc. These triggers provoke reflex vasodilation and bradycardia leading to syncope.

Symptoms of neurally mediated syncope include dizziness, lightheadedness, and fatigue, with prodromal features such as diaphoresis, pallor, palpitations, nausea, hyperventilation, and yawning. Myoclonic jerks may occur when the patient is unconscious and need to be distinguished from seizure activity. If the history is typical, and this is the first episode in a young patient with no suspected heart disease, the patient can be reassured and sent home. If there is a history of infrequent episodes, a tilt-table test and psychiatric evaluation are recommended. Frequent episodes require evaluation with continuous ambulatory electrocardiography. Patients in high-risk occupations should be investigated with the first episode of syncope. Beta-blockers are generally effective treatment.

Orthostatic hypotension: Syncope due to orthostatic hypotension 2° autonomic dysfunction causes symptoms with no increase in the patient's heart rate with standing or during the vertical phase of tilt-table testing.

Typically, try non-pharmacologic therapy first (e.g., support hose and increased salt); but treatment can also include midodrine (ProAmatine®). Midodrine is a prodrug for desglymidodrine, an alpha agonist that stimulates the alpha-adrenergic receptors of both arteriolar and venous vessels. Fludrocortisone, a mineralocorticoid agonist that promotes retention of sodium and water, can also be used but can cause supine hypertension.

Note on the tilt-table test: Monitor patients with continuous ECG and noninvasive BP monitoring. Depending on the protocol, the patient is usually kept supine for 5 minutes, then swung to a more vertical position (60–90°), and kept there 40–60 minutes or until changes in ECG, BP, or symptoms conclude the test with a positive result.

Syncope due to arrhythmias is discussed on page 5-35.

CARDIOMYOPATHIES

There are 3 main types of nonischemic cardiomyopathy: hypertrophic, restrictive, and dilated.

HYPERTROPHIC CARDIOMYOPATHY (HCM)

Hypertrophic cardiomyopathy (HCM) was previously called IHSS: idiopathic hypertrophic subaortic stenosis.

HCM is associated with sudden cardiac death, which is probably due to ventricular arrhythmias. The only cure is cardiac transplant! Sudden cardiac death is most frequent in young patients with the familial form.

Quick Quiz

- Name the side effects associated with amiodarone.
- What determines a toxic level of digoxin?
- For what conditions is the treatment of choice, radiofrequency ablation, guided by EP studies?
- Explain how you approach the diagnostic workup in a patient with probable neurocardiogenic (vasovagal) syncope.
- What are the risk factors for sudden death in patients with HCM?

It is usually an autosomal dominant disease of the heart muscle, characterized by a small left ventricular cavity and marked hypertrophy of the myocardium with myofibril disarray. Patients with HCM usually have left ventricular hypertrophy (LVH), especially in the basal ventricular septum, where disordered myocytes are found (Image 5-10). The hypertrophy is occasionally concentric. The initial problem is diastolic dysfunction. Q waves are often seen on ECG (pseudoinfarct pattern; this can also be seen with WPW).

Patients with HCM often present with a history of exercise-induced syncope or severe dyspnea, but many are asymptomatic. Symptoms may be triggered by hypovolemia, which causes further reduction of LV cavity size.

Bedside with HCM: The patient has a harsh, nonradiating, midsystolic aortic murmur, usually in the left 3rd space, which increases with Valsalva and decreases with sustained handgrip. There is a carotid pulse that has a brisk upstroke, but, because outflow obstruction occurs late in systole, it is bifid in 2/3 of HCM patients. The briskness of the upstroke further distinguishes it from aortic stenosis. Palpation at the apex may surprise you with a double- or triple-tap impulse. A mitral regurgitation murmur can also be heard from systolic anterior motion (SAM) of the mitral valve due to a suction-like effect of the outflow obstruction.

Image 5-10: Hypertrophic cardiomyopathy

The ECG in patients with HCM may be normal, but it often has inferior-to-lateral Q waves (from the hypertrophied septum) and has a normal-to-increased voltage from left ventricular hypertrophy (LVH). If the voltage is low, consider an infiltrative cardiomyopathy, such as amyloid heart disease. Again, confirm diagnosis with an echocardiogram.

Note: Nonsustained ventricular tachycardia (NSVT; < 30 seconds of VT) has an adverse prognostic significance in young patients with HCM.

Diagnose with 2D echo and color Doppler echo. Always do a Holter monitor and an exercise stress test on patients diagnosed with HCM. As just mentioned, a young patient is at even higher risk if the Holter monitor shows nonsustained episodes of VT. The size of the LV outflow gradient is not associated with the risk of sudden cardiac death. Some contend that decreased left ventricular filling from an inflow gradient of the LV may be a more important factor in HCM than the outflow gradient. More recently, cardiac MRI has been used to determine the site and degree of hypertrophy.

Risk factors for sudden death in HCM:

- Septal thickness > 30 mm
- Personal history of syncope
- Family history of sudden death in 1st degree family member
- NSVT on Holter monitor
- Failure to augment systolic BP on treadmill testing (< 10 mmHg increase at peak exercise)

Treatment for HCM

Treatment for HCM:

- **Surgery** for HCM entails removal of part of the ventricular septum, thereby decreasing the outflow gradient; symptoms are relieved, but again, risk of sudden cardiac death after surgery is unchanged.
- **Antiarrhythmic** therapy also does not affect the mortality rate of sudden cardiac death; no known drug improves the mortality rate!
- **Beta-blockers/verapamil** are not recommended for asymptomatic patients, nor patients with demonstrable dynamic obstruction. Otherwise, they are used for symptomatic patients, especially those with chest pain as the dominant symptom. These drugs also improve diastolic filling by slowing heart rate.
- **Amiodarone** is used in cases in which there is a high risk of sudden cardiac death—as in the familial form.
- **RV pacing** can help obstructive symptoms in some patients.
- **Intracoronary injection of ethanol** to cause a controlled septal infarction may reduce the obstruction.
- **Diuretics** are used in HCM only when there is heart failure, and then only with extreme caution!
- **Anything** that decreases LV volume is dangerous in HCM. This includes diuretics, nitrates, and volume depletion.

RESTRICTIVE CARDIOMYOPATHY

Restrictive cardiomyopathy must be differentiated from constrictive pericarditis (page 5-50) because the signs and symptoms may be similar. Although constrictive pericarditis is often quickly treated with good results, restrictive cardiomyopathy is not reversible.

Arrhythmias, such as atrial fibrillation, occur early in the course of these diseases. Constrictive pericarditis is a pericardial problem; restrictive cardiomyopathy is a myocardial problem.

Causes of restrictive cardiomyopathy include amyloidosis, sarcoidosis, hemochromatosis, and lipid storage diseases.

On 2D echocardiogram, the myocardium may be thickened with a granularity, which suggests an infiltrative process.

Thoracotomy is occasionally done to ensure that you do not miss a treatable constrictive pericarditis; these are treated with pericardiectomy.

Treat mild-to-moderate restrictive cardiomyopathy, with diuretics. Remember that digoxin is usually reserved for severe heart failure. It is used in restrictive cardiomyopathy only as an antiarrhythmic—for treatment of associated A. fib.

DILATED CARDIOMYOPATHY

Patients with dilated cardiomyopathy (previously "congestive") have symptoms of right and left heart failure. Usually, there is a slow onset of symptoms—months to years. The course is mediated by treatment, but it usually slowly progresses, within 3 years, to death.

Hypertension and ischemia are the most common etiologies of dilated cardiomyopathy.

Etiology of nonischemic cardiomyopathy:

- Idiopathic (probably viral—most common)
- Alcohol
- Cocaine
- Amphetamines
- Organic solvents ("glue sniffers" heart)
- Cancer chemotherapy
- Late hemochromatosis
- Familial
- Deficiencies of selenium and carnitine

Think Chagas disease in patients from Central and South American countries.

In pregnant women, a "peripartum cardiomyopathy" can occur anytime from the beginning of the last trimester through the first 6 months postpartum.

Patients with dilated cardiomyopathy can form mural thrombi with arterial embolization (2% occurrence).

Treatment for all dilated cardiomyopathy: Treat the underlying cause and consider chronic warfarin anticoagulation. Consider anticoagulation even if there is no mural thrombus because of the devastating effects of both systemic embolization and pulmonary embolization (to which these patients are also susceptible).

Heart failure due to dilated cardiomyopathy is treated similarly to other LVFs (see below). A combination of a diuretic, ACE inhibitor/ARB, and beta-blockers is the usual therapy. Aldosterone antagonists (e.g., spironolactone) may also be used.

HEART FAILURE

OVERVIEW

A newer definition of heart failure (HF) calls it a complex clinical syndrome resulting from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood.

There are many ways to classify HF:

- Low-output or High-output
- Acute or Chronic
- Systolic or Diastolic
- Left-sided or Right-sided

Cardiac output is well maintained in mild HF, usually at the expense of increased left ventricular end-diastolic volume (LVEDV) and increased heart rate.

Numerous adaptations occur in response to heart failure in the peripheral circulation, kidney, skeletal muscle, and other organs. The changes contribute to the overall clinical manifestations and ultimately become maladaptive.

In response to exercise, LVEDV and plasma norepinephrine rise more than in controls, but the resulting cardiac output increase does not rise in proportion to O_2 consumption—so the patient has dyspnea on exertion and is easily fatigued. The adrenergic system and the renin-angiotensin-aldosterone system play a major role in progression of heart failure and maladaptive mechanisms.

LOW-OUTPUT HF

NYHA Classification

NYHA (New York Heart Association) classification of heart failure (classes and definitions) is a functional classification based on how much the patient is limited during physical activity. In clinical use, it is being superseded by the ACC/AHA classification (next):

Class I: Cardiac disease but no limitation in physical activity.

Class II: Slight limitation of normal physical activity (fatigue, palpitations, dyspnea, and/or angina). Comfortable at rest.

Class III: Marked limitation of physical activity. Slight activity causes symptoms. Still comfortable at rest.

QuickQuiz

- Define Stage A through Stage D Heart Failure (ACC/AHA classification). What are the goals of therapy for each of these stages?
- What is the sequence of drugs used to treat HF based on ACC/AHA Stage?
- What factors are associated with poor prognosis in HF?

Class IV: Symptoms may be present at rest. Unable to carry on any physical activity without discomfort.

ACC / AHA Classification

The 2005 ACC/AHA staging system for HF shows heart failure as more of a progressive disorder and has goals of therapy for each stage (A through D). Know the definition, goal of therapy, and medications for each stage of HF.

Stage A HF patients are at risk for heart failure but have no structural heart disease and include those with hypertension (HTN), atherosclerotic heart disease, diabetes, and metabolic syndrome. Stage A also includes any asymptomatic patient using cardiotoxins (such as anthracycline) or with a family history of cardiomyopathy.

So yes, you read this right: Just having HTN means you have Stage A heart failure!

Goals for Stage A therapy are to treat the disorder (HTN, lipid disorder, metabolic syndrome), encourage exercise, and discourage alcohol/illicit drug use.

Stage A drugs are ACEI/ARBs for all!

Stage B HF patients have structural heart disease but without signs or symptoms of heart failure. This stage includes patients who have a history of a previous MI and those with LV remodeling from LVH or low LVEF—and, of course, those with asymptomatic valvular heart disease.

Goals of Stage B therapy are the same as those listed under Stage A.

Stage B drugs are:

- beta-blockers, in addition to
- ACEI/ARBs as used in Stage A.

Use implantable defibrillators if indicated.

Stage C HF patients have structural heart disease with prior or current symptoms of heart failure. These are patients with structural heart disease as described above in Stage B, who additionally have signs and symptoms of HF (e.g., dyspnea, fatigue, and decreased exercise tolerance).

Goals for Stage C therapy are, again, the same as Stages A and B, but add dietary salt restriction.

Stage C drugs are:

- diuretics for fluid retention, in addition to
- beta-blockers as used in Stage B, and
- ACEI/ARBs as used in Stage A.

Selected patients with Stage C may need:

- aldosterone antagonists,
- ARBs combined with ACEI,
- digoxin, or
- hydralazine/nitrates.

Biventricular pacing and/or implantable defibrillators are used as needed.

Stage D HF patients have marked symptoms at rest in spite of maximal medical therapy. These patients typically have frequent hospitalizations and commonly cannot be discharged without special interventions.

Goals for Stage D therapy are to discuss end-of-life issues in addition to the goals for Stage C.

Stage D drugs are the same as those for Stage C.

Options for Stage D patients include hospice care and consideration of "extraordinary measures," including heart transplant, chronic inotropes, permanent mechanical support (ventricular assist devices), and experimental drugs or experimental surgery.

The most common causes of low-output HF are:

- coronary artery disease (40%—although recent data pushes this to near 60% of etiologies),
- dilated cardiomyopathy (30%),
- valvular disease (15%), and
- hypertension (10%).

It is the most common diagnosis in hospitalized elderly patients. Only 50% of patients with HF die from actual heart muscle failure; ~ 40% die from arrhythmias!

Determining Prognosis in HF

In severe HF, a worse prognosis is associated with:

- Low ejection fraction
- Low sodium
- High BUN
- Low potassium
- High or low magnesium
- High norepinephrine and catecholamine levels

Exercise tolerance is not closely associated with prognosis. The Seattle Heart Failure Model (a validated online tool) can provide a reasonable "ballpark" estimate of HF prognosis based on standard clinical data.

Mechanism of HF

Low-output ventricular failure results in decreased cardiac output. This in turn causes an increased A-a O_2

difference and decreased renal perfusion. The decreased cardiac output may be due to systolic dysfunction, systolic + diastolic dysfunction, and, sometimes, diastolic dysfunction. (Diastolic dysfunction may have normal cardiac output—see below.) After a certain point, decreased cardiac output from any type of HF causes decreased renal perfusion. This stimulates the release of renin, which allows the conversion of angiotensinogen to angiotensin I. Angiotensin I is converted to angiotensin II in the lungs. Angiotensin II then stimulates the secretion of aldosterone, which then causes retention of Na^+ and water, causing a greatly increased filling pressure (moving the Starling curve to the right).

Let's see if we have all that: Low CO → low renal perfusion → high renin → high angiotensin I → high angiotensin II → high aldosterone → retention of Na^+ → retention of water → high filling pressure → exacerbation of HF (Figure 5-6). The increased heart rate in HF is due to both an increased sympathetic tone and an increased level of catecholamines in an attempt to compensate for reduced stroke volume. The higher the catecholamine pool, the worse the prognosis.

ADH is released from the hypothalamus but has a minor effect.

Atrial (or A-type) natriuretic peptide (ANP) and brain natriuretic peptide (BNP; also called B-type natriuretic peptide) are released from the heart myocytes; the release is stimulated by stretching of the atrium (ANP and BNP) and the ventricle (BNP). These peptides are released in an attempt to offset the effects of renin angiotensin and ADH but cannot antagonize them adequately. ANP and BNP increase excretion of sodium and water, cause vasodilation, and inhibit the effects of aldosterone.

In severe heart failure, the BNP increases 20- to 100-fold. High levels of these peptides (especially BNP) actually correlate directly with a poor prognosis in HF. BNP is also elevated in restrictive cardiomyopathy but not constrictive pericarditis and is used to differentiate between these disorders.

About 30–50% or more of CHFs are caused by diastolic dysfunction (more recently termed heart failure with preserved LV function) rather than systolic dysfunction.

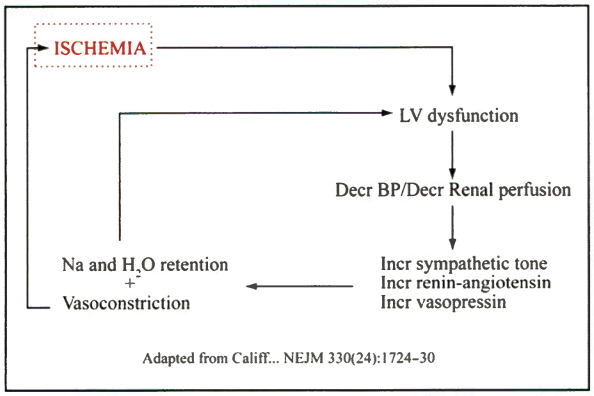


Figure 5-6: Spiral of Worsening HF

Myocardial ischemia, severe concentric LVH, HCM, and diabetic cardiomyopathy cause diastolic dysfunction, at least initially. With diastolic dysfunction, the CO is often normal; HF develops from increased filling pressure (from decreased relaxation due to increased stiffness). So the problem is not that the ventricle is not squeezing enough, but rather that it is not relaxing enough. This is reflected in an elevated LVEDP and RVEDP, tachycardia, and an S_4.

Treatment for HF

General Measures

See above for treatment according to ACC/AHA stage. We will now discuss the individual drugs and how they affect/improve survival in heart failure.

[Note: In our discussion the term Class refers to NYHA classification; the term Stage refers to the ACC/AHA classification.]

Current pharmacologic management of low-output heart failure is aimed at reducing ventricular preload and afterload as well as diminishing, inhibiting, and/or antagonizing neurohormonal vasoconstrictor activation, rather than directly increasing cardiac contractility as in the past.

The optimal treatment of heart failure aggressively addresses the major risk factors including hypertension, diabetes, obesity, metabolic syndrome, hyperlipidemia, and coronary artery disease (CAD). Therapies that promote regression of LVH or reverse remodeling of the dilated heart should be used; these include inhibitors of catecholamines and the renin-angiotensin-aldosterone pathway.

ACE Inhibitors and ARBs

Angiotensin-converting enzyme (ACE) inhibitors (ACEIs; captopril, enalapril, lisinopril, benazepril, fosinopril, quinapril, ramipril) are 1st line therapy. These are great drugs! They decrease systemic vascular resistance, pulmonary capillary wedge pressure, right atrial pressure, and end-diastolic and end-systolic dimensions; and they improve cardiac performance, as evidenced by increased cardiac output and stroke volume, and by improved fractional shortening, as determined by echocardiography. Hence, they decrease tachycardia due to HF.

ACEIs block formation of angiotensin II. They also decrease the incidence of ventricular arrhythmia and prolong survival. In addition, they reverse the remodeling in the myocytes, which causes progression of heart failure.

Angiotensin II receptor blockers (ARBs) block the effect of angiotensin II at the cell wall. ARBs are given in place of ACEIs and are equally effective (commonly grouped as "ACEI/ARB"). Sometimes ARBs are given as additive therapy to ACEIs in severe, refractory heart failure.

QuickQuiz

- What is the sequence of events that worsens HF?
- When are beta-blockers started in the treatment of HF?
- With what type of HF do aldosterone antagonists prolong survival?

ARBs cause less cough than ACEIs and are often given when patients develop refractory cough on ACEIs.

Monitor patients on ARBs for renal impairment and hyperkalemia.

Commonly used ARBs:

- Candesartan (Atacand®)*
- Irbesartan (Avapro®)
- Olmesartan (Benicar®)
- Valsartan (Diovan®)*
- Eprosartan (Teveten®)
- Losartan (Cozaar®)
- Telmisartan (Micardis®)

* = RCT data show mortality benefit in heart failure.

Beta-blockers

Beta-blockers are now part of standard heart failure treatment. Usually, start beta-blockers on patients with Stage B after they are stabilized on ACEIs. In HF, the sympathetic nervous system is overstimulated. This raises norepinephrine levels, which can cause cardiac remodeling, lead to arrhythmias, and increase mortality risk. Mortality is clearly improved by carvedilol (~ 65% relative risk reduction), metoprolol, and bisoprolol (~ 35%).

Previously, it was taught that starting these drugs while patients are decompensated is contraindicated. Current guidelines recommend initiation of beta blockade at any stage of heart failure, once adequate diuresis has been achieved. Carvedilol (Coreg®) is a nonselective beta-blocker that also has some alpha-blocker effect. Use in conjunction with ACE inhibitors and diuretics to treat Class II–III heart failure.

Diuretics

Diuretics are given if needed for volume control (i.e., decrease edema and pulmonary congestion) during Stage C therapy. Remember: Therapy now begins with ACEI/ARBs before patients even have symptoms (Stage A).

Diuretics are effective in both systolic and diastolic ventricular failure for symptom control. All but the aldosterone antagonist diuretics have no mortality benefit, unlike ACEI/ARBs and beta-blockers.

If a loop diuretic given twice daily in doses equivalent to furosemide 100 to 200 mg/d is inadequate, a thiazide diuretic or metolazone may be added, which results in a synergistic effect. This combination also results in severe hypokalemia and prerenal azotemia, so close monitoring is necessary.

Aldosterone antagonists prolong survival in some HF patients with low EF:

- **Spironolactone** showed a 30% decrease in mortality at 24 months when given to patients with Class IV HF or Class III having had Class IV in the previous 6 months (RALES trial).
- **Eplerenone** showed a 15% decrease in mortality at 16 months in patients with recent MI and EF < 40% and evidence of HF or diabetes mellitus (EPHESUS trial). Patients need to be closely monitored for hyperkalemia.

More notes on diuretics:

Thiazides mainly block Na^+ and Cl^- resorption in the distal convoluted tubule and, to a minor extent, block Na^+ resorption in the proximal tubule. Examples are hydrochlorothiazide and metolazone (Zaroxolyn®).

Spironolactone competitively inhibits aldosterone (so, is K^+ sparing) and is being used increasingly in the management of chronic heart failure (RALES trial).

Furosemide (Lasix®), bumetanide (Bumex®), torsemide (Demadex®), and ethacrynic acid are the loop diuretics. They block Na^+ resorption in the ascending limb of the loop of Henle. Bumetanide may also have some action on the proximal tubule.

Indapamide (Lozol®, Lozide®) has an unknown mechanism of action. It has an anti-hypertensive effect occurring far below the antidiuretic effect. Probably has renal and extrarenal effects.

Triamterene has an unknown mechanism of action.

With azotemia, do not use spironolactone or triamterene because these may cause hyperkalemia; thiazides are not effective, but furosemide usually is. Much more on this in the Nephrology section, Book 2.

Digoxin

Digoxin is effective only in severe systolic ventricular failure and is usually started for Stage C. It is started after the above therapies are established and the patient is still symptomatic. Recommendations are for EF < 40% with Class II, III, or IV symptoms despite ACEI, beta-blocker, and diuretic. In HF, digoxin appears to reset the baroreceptors and dampen the renin-angiotensin effects; it has very little inotropic effect. It is also used to control the ventricular rate in a patient with HF and atrial fibrillation. Digoxin has no mortality benefit, but it does improve symptoms and decrease hospitalizations. See Table 5-11 for drugs that increase digoxin level.

Nitrates

Nitrates are occasionally used next (good venodilator, moderate arterial dilator)—remember the nightly 6-hour nitrate-free window to prevent tolerance (discussed under Cardiac Ischemia on page 5-8).

Table 5-11: Drugs that Increase Digoxin Level
Alprazolam
Amiodarone
Abx: Macrolides and tetracycline
Cyclosporine
Diphenoxylate or propantheline (decrease bowel motility)
Indomethacin
Itraconazole (antifungal)
Omeprazole
Propafenone (class Ic antiarrhythmic)
Quinine
Spironolactone

With ventricular failure, patients can have increased systemic (peripheral) vascular resistance (SVR) with a normal or low BP, and they still benefit from an arteriolar vasodilator.

Nitrates plus hydralazine are recommended for patients intolerant to ACE inhibitors and ARBs. In the African-American heart failure population, this combination is recommended as adjunctive therapy to ACE inhibitors (or ARBs) and beta-blockers to further reduce mortality (A-HeFT trial).

Anticoagulation

HF patients with an ejection fraction < 25% are often placed on chronic anticoagulation empirically due to increased risk of mural thrombus. However, this is controversial because there are no randomized controlled trials of chronic anticoagulation in heart failure that demonstrate convincing benefit. Clinical practice guidelines recommend anticoagulation in heart failure patients with chronic atrial fibrillation, history of systemic or pulmonary embolism, or a mobile left ventricular thrombus.

Other Therapy

Current guidelines recommend the use of an implantable cardioverter defibrillator (ICD) as primary prevention of all-cause mortality in NYHA Class II and Class III patients with left ventricular ejection fractions (EFs) of ≤ 30% and either ischemic or nonischemic cardiomyopathy.

Ventricular dyssynchrony is electrical disturbances that cause the heart to pump blood in an inefficient way. It is suggested by the findings of decreased ejection fraction with narrow QRS complexes. Use echocardiography to detect ventricular dyssynchrony. A positive Doppler echo shows delay between septal and lateral systolic wall velocity.

Cardiac resynchronization therapy (CRT) has been recommended for patients with:

- EF ≤ 35% with normal sinus rhythm, or
- NYHA functional Class III with ventricular dyssynchrony despite optimal medical therapy.

Emergency Treatment for Severe Heart Failure

[Know.] With severe ventricular failure, patients may require short-term treatment with inotropes (dopamine, dobutamine, and milrinone):

Dopamine:

- At < 2 μg/kg/min dopamine stimulates the dopaminergic receptors and causes mesenteric dilation.
- At 2–5 μg/kg/min, it has a predominantly beta-agonist effect (positive inotropy) and increases renal perfusion.
- At > 10 μg/kg/min, it mainly has an alpha-agonist effect and causes vasoconstriction. Generally never use > 10 μg/kg/min!

Dobutamine is another inotropic agent that can be used for severe ventricular failure. It does not have the vasoconstrictor activity of dopamine and actually has some vasodilatory effects. Dobutamine is sometimes used for outpatient therapy.

Milrinone (Primacor®) is an inotropic/vasodilator agent with phosphodiesterase inhibitor activity (peak III cAMP—an isoenzyme of cAMP). It is also indicated for short-term IV treatment of HF. It does not cause thrombocytopenia (unlike amrinone), and it is not associated with tachycardia.

Additionally, afterload and preload reducers are used:

Hydralazine is an afterload reducer (arterial vasodilator); it also increases heart rate. Hydralazine is frequently used with nitrates to get the added benefit of decreased preload. Rarely used: Prazosin and minoxidil are also afterload reducers but are associated with rapid development of tolerance and fluid retention. Nitroprusside is not used much now because of tolerance and toxicity problems.

Hydralazine and isosorbide dinitrate combination was shown to increase survival in the VHeFT (vs. placebo) and AHeFT (as an adjunct to standard therapy in African-Americans) studies.

Coronary artery bypass improves the outcome in HF only when the HF is due to mitral regurgitation caused by an ischemic papillary muscle. For end-stage HF, cardiac transplant is the best option. There is a 65% 5-year survival and a 55% 10-year survival!

HIGH-OUTPUT HF

"High-output" ventricular failure is seen with peripheral shunting (large AV fistulas, severe hepatic

QuickQuiz

- In what patient group has nitrates plus hydralazine proven beneficial?
- What does dopamine do at low doses (< 2 µg/kg/min)? At doses of 2–5 µg/kg/min?
- Know all drugs used to treat HF!
- With what diseases does high-output heart failure occur?
- What is the treatment for acute pulmonary edema?

hemangiomatosis, and Paget disease!) and low-systemic vascular resistance, as seen in gram-negative sepsis. You can also see it in patients with hyperthyroidism, beriberi, carcinoid, or anemia. Remember, though, these patients often have a normal cardiac output at the time of diagnosis—because of the worsening ventricular failure!

RIGHT VENTRICULAR FAILURE

"The most common cause of right heart failure is left heart failure!" is what you heard on rounds. And, indeed, right ventricular failure (RVF) is mainly caused by pulmonary hypertension (1° or 2°)—usually secondary to LVF. RVF is also seen with large RV infarctions and cor pulmonale. Remember: If the patient has signs of RVF (JVD and liver congestion), but pressures are the same in all chambers in diastole, think external compression (constriction or effusion).

Orthopnea: As LVF progresses, orthopnea usually worsens, but it may then actually improve temporarily as RV function worsens due to the pulmonary hypertension.

Paroxysmal nocturnal dyspnea does not improve with sitting up, as orthopnea does.

PULMONARY EDEMA

Immediate treatment for acute pulmonary edema:

- Patient should be sitting with legs dangling, if possible, to decrease venous return.
- Give 100% O_2, morphine (to decrease anxiety and decrease vasoconstriction).
- Give furosemide (causes venodilation even before the diuresis).
- IV nitroglycerin or nitroprusside can be used if systolic BP is > 100.
- Strongly consider the use of dobutamine if systolic BP < 90.
- Aminophylline is rarely used to increase respiratory muscle function.

PERICARDIAL DISEASES

NON-CONSTRICTIVE PERICARDITIS

90% of non-constrictive pericarditis is idiopathic and probably viral in origin; often, there is a preceding URI or gastroenteritis.

Causes of non-constrictive pericarditis:

- Idiopathic (90%), probably viral
- Tuberculosis
- Connective tissue diseases
- Sepsis
- Renal failure (uremic)
- Cancer
- Postradiation
- Hypothyroidism
- MI (Dressler syndrome)
- Open heart surgery (postpericardiotomy syndrome)
- Certain drugs, especially procainamide and hydralazine

Suspect TB as the cause if the patient is at high risk, or if the symptoms of pericarditis do not resolve after 2 weeks of treatment.

Both Dressler syndrome and postpericardiotomy syndrome are autoimmune processes that occur several weeks after the precipitating event. Even if the history is very suggestive, you must consider the following entities and exclude them to make the diagnosis: MI, pulmonary embolus, and endocarditis. Other causes include uremia and connective tissue disease.

Patients with pericarditis usually present with very severe chest pain, sometimes pleuritic, which (classically) improves when leaning forward. The pain is retrosternal and left precordial, and referred to the neck, arms, or left shoulder. Usually, the patient has some fever and tachycardia. A pericardial friction rub, which does not always occur and may be evanescent, is diagnostic for pericarditis.

The ECG may show diffuse concave-up ST elevation (vs. localized, concave-down ST elevation in an acute MI) and, occasionally, depressed PR segments, especially in lead II. ECG changes occur in 4 stages:

- Stage 1: diffuse ST elevation segments with upward concavity with PR depression.
- Stage 2: normalization of ST segments after several days.
- Stage 3: inverted T waves.
- Stage 4: Weeks or months after the onset of acute pericarditis, the ECG returns to normal.

Pericarditis can cause transient increases in CKMB (secondary to associated myocarditis). This is especially likely if you see T-wave inversion (without the ST elevation).

Treat pericarditis by stopping any possible causative drugs and giving NSAIDs. Do not treat idiopathic pericarditis with steroids because there may be a relapse when they are stopped. Treatment with colchicine has been shown to reduce recurrence. TB pericarditis is treated with glucocorticoids.

CONSTRICTIVE PERICARDITIS

It occurs when resorption of pericardial effusion is followed by obliteration of the pericardial cavity with scarring. Constrictive pericarditis must be differentiated from restrictive cardiomyopathy (page 5-44) because the signs and symptoms may be similar.

(Again: Although constrictive pericarditis is often quickly treated with good results, restrictive cardiomyopathy is not reversible.)

Constrictive pericarditis may follow:

- Viral or idiopathic pericarditis
- Traumatic hemopericardium
- Tuberculosis
- Cardiac surgery
- Mediastinal irradiation
- Purulent infection
- Histoplasmosis
- Rheumatoid arthritis
- SLE
- Neoplastic disease (especially breast cancer, lung cancer, and lymphoma)
- Chronic renal failure with uremia treated by chronic dialysis

In constrictive pericarditis, ventricular filling is normal during early diastole but reduced abruptly when the elastic limit of the pericardium is reached.

Constrictive pericarditis is characterized by a rapid, early, diastolic filling of the LV, causing a loud presystolic knock just after S_2. Pulsus paradoxus can occur but is usually mild.

There are 2 clinical hallmarks of constrictive pericarditis:

- Kussmaul sign: When, because the heart is encased in a "shell," the negative pressure during inspiration is transferred to the venous inflow tract, resulting in a lack of the normal decrease in jugular venous distention (JVD) during inspiration; when severe, JVD can increase even during inspiration.
- Large, right-sided *x* and *y* descents. This is seen as a brisk collapse of the jugular veins during diastole.

Constrictive pericarditis can cause calcification of the pericardium (~ 50%). You can see this best on the lateral chest x-ray because it is typically found over the right ventricle, but you can also see it on the PA view and on CT. A lateral chest x-ray that shows calcification over the right ventricle is pathognomic for constrictive pericarditis.

CT and MRI are best for measuring thickness of pericardium, but echo is also used. A pericardial thickness of > 5 mm is suggestive of, but not sufficient for, diagnosis. The pericardium can be of normal thickness in ~ 20–25% of cases of constrictive pericarditis.

In both tamponade and constrictive pericarditis, cardiac cath shows the same pressure during diastole in all 4 chambers. You can often make the differentiation between tamponade and constrictive pericarditis at the bedside using these hallmark signs (see tamponade below). Constrictive pericarditis must be treated with an open thoracotomy and pericardiectomy. Unfortunately, this resolves the problem only 50% of the time!

Brain natriuretic peptide (BNP) plasma levels are being used to differentiate between constrictive pericarditis and restrictive cardiomyopathy. BNP increases with heart failure. With restrictive cardiomyopathy, there is a component of HF, and BNP levels are markedly elevated (e.g., 8x max normal). With constrictive pericarditis, there is little or no actual HF, and BNP levels are typically just above normal.

RECURRENT PERICARDITIS

Recurrent pericarditis is a condition in which the only disabling problem is the associated chest pain. It does not progress to constrictive pericarditis. It is only rarely associated with arrhythmias. NSAIDs, colchicine, and glucocorticoids are used to treat it. Pericardiectomy often does not have good results and is tried only after medical treatment options have been exhausted.

PERICARDIAL EFFUSION

Pericardial effusion is usually diagnosed with an echocardiogram, but CT and MRI are the most accurate, especially if the resultant tamponade is due to localized pockets of effusion. Surgical drainage is preferable in traumatic hemopericardium, post-surgical effusion, and when bacteria or TB is suspected as the cause of tamponade. On the other hand, pericardiocentesis rarely helps in diagnosis but is often used to treat viral, idiopathic, neoplastic, hypothyroid, and renal failure-related tamponade. Pericardial window biopsy can help diagnose TB. Sometimes, you need an endomyocardial biopsy to differentiate constrictive vs. restrictive etiology. If pericardiocentesis fluid is diagnostic in acute pericardial effusion in an otherwise normal person, it usually is due to a neoplasm! (Read this sentence again—it's a little tricky.)

Tamponade [Know!] is a critical cardiovascular compromise caused by a pericardial effusion. There is obstruction to the inflow of blood to the ventricles. The most common causes are trauma, cancer, uremia, and acute pericarditis. When there is rupture of the free wall of the heart, as in trauma or post-MI, tamponade develops quickly; otherwise, it usually develops slowly.

QuickQuiz

- What are the 2 clinical hallmarks of constrictive pericarditis?
- When is the measured diastolic pressure of all 4 chambers equal?
- How is BNP used to differentiate constrictive pericarditis from restrictive pericarditis?
- Name the 3 hallmarks of cardiac tamponade.
- When should surgery be performed for a secundum ASD?

The 3 hallmarks of acute tamponade:

1) Hypotension and muffled heart sounds
2) Pulsus paradoxus (systolic BP drops > 10 mmHg during inspiration)
3) Jugular venous distention with no collapse during diastole (i.e., an attenuated *y* descent)

Tamponade causes soft, distant, heart sounds. Compare and know the difference between this and constrictive pericarditis (above).

CONGENITAL HEART DISEASE

NOTE

Most adult patients with congenital heart disease are asymptomatic! Know that the magnitude of any shunt does not depend on the total blood flow rate, but it is usually a constant ratio of pulmonic to systemic flow (Qp/Qs).

ASD

Ostium Secundum ASD

Secundum atrial septal defect comprises 70% of all atrial septal defects (ASD). It is the most common congenital heart disease found initially in adults (F > M), excluding a bicuspid aortic valve. With a large secundum ASD, there is a systolic ejection murmur (SEM) at the left sternal border (2° to increased flow across the pulmonic valve), occasionally a diastolic murmur (from increased flow across the tricuspid valve), and a fixed split S_2. The left-to-right shunt causes diastolic overloading of the right ventricle and increased pulmonary blood flow with inspiration and expiration.

ECG shows right axis deviation and/or RBBB. Chest x-ray shows an enlarged RV with shunt vasculature. Notice all of the right-sided stuff with ASD—makes sense because ASD causes a volume load on the right side of the heart. Patients may develop 2° atrial fibrillation.

Standard treatment had been open surgical closure, but now most secundum ASDs are closed percutaneously. If there is a > 2:1 left-to-right (pulmonary/systemic) shunt, a surgical closure is done, even if the patient is asymptomatic. In this case, the ASD would eventually cause an increase in pulmonary vascular resistance and associated complications.

Generally, severe, fixed pulmonary hypertension is considered a contraindication to surgical repair of the ASD.

Ostium Primum ASD

This form of ASD is seen most commonly in Down syndrome. Patients with ostium primum atrial septal defect may have a loud pansystolic murmur 2° to mitral and/or tricuspid regurgitation. The regurgitation is due to the ostium being low on the septum, interfering with the function of the AV valves or left mitral valve. ECG has left axis and RBBB.

Surgery for any type of ASD essentially cures the problem. Functional Class III and IV patients can revert to functional Class I with excellent survival! Eisenmenger syndrome is a contraindication to ASD surgery (page 5-52).

Sinus Venosus ASD

Sinus venosus ASD is associated with anomalous pulmonary venous return because it occurs high on the septum. It is a cause of 10% of ASDs.

PDA

Adult patients with patent ductus arteriosus (PDA) are usually asymptomatic. Females > males. PDAs are usually detected early by detection of the distinct murmur. Endarteritis can occur in PDA.

PDA causes a continuous, "machinery" murmur at the LUSB. As pulmonary pressures rise, the murmur becomes less continuous. Differential cyanosis (e.g., develop clubbed toes, normal fingers) with pulmonary hypertension is possible.

Chest x-ray shows calcification of the ductus arteriosus in adults.

If the patient develops pulmonary hypertension, consider Eisenmenger syndrome (see page 5-52).

Surgical or percutaneous closure in symptomatic patients has excellent results. Elderly patients also benefit from surgery.

PULMONARY STENOSIS

Balloon valvuloplasty is the procedure of choice for treating pulmonary stenosis. It has favorable long-term clinical and hemodynamic results.

VSD

Ventricular septal defects are the most common congenital defect in children. They are uncommon in adults because most have either closed spontaneously or have been surgically closed in childhood. 80% of small VSDs close spontaneously in the first 10 years of life. Large VSDs usually require surgery (although even 10% of these eventually close spontaneously). A loud holosystolic murmur is heard at the left lower sternal border.

COARCTATION OF THE AORTA

Know that a bicuspid aortic valve occurs in ~ 70% of patients with coarctation of the aorta! Other associated anomalies include mitral valve problems, left ventricular myocardium problems, and membranes in the left atrium. Notice that all of the heart problems associated with coarctation of the aorta are left-sided! The classic physical findings are either a delayed femoral/brachial pulse (feeling the brachial and femoral pulses, there is a distinct delay in femoral pulse) or an absent femoral pulse. Patients may have an upper-body hypertension and can get hypertensive aneurysmal dilatation and rupture of the circle of Willis. Chest x-ray may show rib notching due to the collateral vessels getting very large and eroding the ribs. Turner syndrome is associated with coarctation of the aorta and a bicuspid aortic valve.

ANOMALOUS CORONARY ARTERY

Pre-mortem detection is extremely difficult and requires a high index of suspicion. This may present as exertional chest pain or exertional syncope in a young otherwise healthy individual. Syncope after exercise can occur in "normal" people, but syncope during exercise is never normal.

SUDDEN DEATH IN EXERCISING YOUNG PEOPLE

The most common cause of death in an exercising young person is HCM (36%). Next most common are coronary anomalies (19%)—although this is a more likely cause in the 30–40-year-old group. With anomalous coronary artery, there is an abnormal course of 1 of the 2 coronary arteries between the 2 great vessels, the pulmonary artery and aorta. At rest, there is plenty of room for the vessel to pass without compromise; however, in extreme exercise, the cardiac output can increase 4–8-fold. This expands the elastic pulmonary artery and aorta, resulting in compression of the coronary artery as it courses between the great vessels. This compression creates coronary ischemia and arrhythmias.

Also consider primary pulmonary hypertension as the cause in young women.

Other etiologies of sudden death in exercising young people include:

- Cardiac hypertrophy (10%)
- Ruptured aorta (5%)
- Intramyocardial course of the LAD (5%)
- Aortic stenosis (4%)

OTHER

Marfan syndrome causes decreased strength of the aorta (with aortic regurgitation and dissection) and MR. Rubella causes congenital pulmonic stenosis, PDA, and multiple pulmonary artery stenoses. Cystic fibrosis can eventually cause pulmonary hypertension.

PULMONARY HEART DISEASE

COPD AND SLEEP APNEA

The most common causes of pulmonary heart disease are COPD and sleep apnea syndrome. These two are covered extensively in the Pulmonary Medicine section, Book 2, so we will cover the other causes here.

EISENMENGER SYNDROME

Eisenmenger syndrome occurs in patients with a large, intracardiac shunt when the pulmonary vascular resistance becomes greater than systemic vascular resistance—so, the shunt becomes right-to-left instead of the more normal left-to-right. It is a result of severe pulmonary hypertension, which can develop early (or late) in patients with large, cardiac, left-to-right shunts of virtually any type: VSDs, PDAs, and ASDs. Cyanosis is common. Heart-lung transplant is the only effective treatment for Eisenmenger syndrome.

CHRONIC THROMBOEMBOLIC OBSTRUCTION

Chronic thromboembolic obstruction usually occurs as a result of impaired fibrinolytic resolution of acute thromboembolism, leading to organization, incomplete recanalization, and chronic obstruction of the pulmonary vascular bed. Most patients treated for acute pulmonary thromboembolism do not develop chronic pulmonary hypertension. Chronic thromboembolic obstruction is also the result of other causes of secondary pulmonary hypertension such as large left-to-right shunts, and chronic LVF.

Progression of this disease probably results from the pulmonary arteriolar changes (instead of more PEs); these are similar to the changes that develop with large septal defects. The resultant increased pulmonary vascular resistance causes RVF. Surgical removal of the thromboembolic material results in significant improvement. Vena cava filters may be used in patients with DVT. Anticoagulate.

QuickQuiz

- What are the 2 most common causes of sudden death in an exercising young person? What third cause do you consider in young women but not in young men?
- What are the 2 cardiac-related absolute contraindications to pregnancy?

PULMONARY ARTERIAL HYPERTENSION

Note that the terms for this disease are changing. Previously it was called idiopathic pulmonary hypertension, and before that, primary pulmonary hypertension. The World Health Organization has reorganized causes of pulmonary hypertension into 5 groups of which IPH is now part of Group 1: Pulmonary arterial hypertension (PAH).

PAH includes the "sporadic idiopathic pulmonary hypertension" that usually occurs in young women, is refractory, and results in death within 5–10 years.

Treatment: Calcium channel blockers (in patients who are "reactive" to vasodilator testing) and sildenafil (Viagra®, Revatio®) are helpful. Endothelin antagonists and prostacyclins may also be of use. Heart-lung transplant is occasionally used.

It is important to differentiate between 1° and 2° because surgery may help 2° PAH. A heart catheterization rules out secondary causes such as R-to-L shunt and chronic LVF. A perfusion lung scan rules out PE. PCWP is, of course, increased only in the pulmonary hypertension caused by, or concurrent with, LVF.

PREGNANCY AND THE HEART

Pregnancy: Absolute contraindications to pregnancy include PAH and Eisenmenger syndrome (particularly deadly if cyanosis is present), both discussed above. In secundum ASD, aortic stenosis, and dilated cardiomyopathy, the patient must be closely watched. In aortic stenosis and dilated cardiomyopathy, patients are usually kept at bed rest. Secundum ASD patients are usually not at risk for cardiac decompensation, unless they develop atrial fibrillation.

Warfarin is contraindicated in pregnancy due to its teratogenic effects. It is absolutely contraindicated in the 1st trimester; although, to be safe, most physicians do not give it at all during pregnancy. Heparin, LMWH, digoxin, quinidine, propranolol, calcium channel blockers, and DC cardioversion are not contraindicated. Although heparin is not contraindicated, it does cause increased morbidity and mortality in mother and child.

A maternal rubella infection during pregnancy is a common cause of supravalvular aortic stenosis, pulmonic stenosis, and other congenital cardiac defects.

Most pregnant women experience some pedal edema. Flow murmurs and S_3 gallops are also common, and the jugular venous pressure increases. Remember to rule out both mitral stenosis and secundum ASD in the pregnant patient presenting with new-onset atrial fibrillation and pulmonary edema.

THE ELECTROCARDIOGRAM

THE 12-LEAD ECG

First, we will briefly go over the basics of ECGs. Refer to Figure 5-7 as we go through this.

A lead tracing is positive if the wave of depolarization spreads toward the positive pole of that lead, and it is negative if it spreads away from the positive pole. The tracing is zero if the wave spreads at a 90° angle to it. For instance, if II is zero, look for the maximum projection to be at aVL (either + or –).

With the 12-lead ECG, the wave of depolarization is recorded on both the frontal and horizontal planes and gives a 3-dimensional representation of the heart. The projection of the electrical activity of the heart onto the frontal plane is recorded by the frontal leads I, II, III, aVR, aVL, and aVF. On the horizontal plane, it is recorded via electrodes placed in the V1-V6 position. Occasionally, a V3R and V4R (placed same as V3 and V4, except on the right side of the chest) are used to better monitor the right side of the heart (e.g., right-sided ischemia). Depolarization moving toward the lead causes a positive deflection (P wave and QRS), as does repolarization moving away from the lead (T wave).

The frontal leads give inferior-superior-left-right information. For example, II, III, and aVF cover the inferior area. ST variations/Q waves occur in these leads with inferior ischemia and infarction.

The horizontal leads relay anterior-posterior-lateral information. Think of V1 as looking at the right side of the heart while V6 looks at the left side. The QRS in V1 is positive when the right ventricle (RV) is depolarizing (and negative when the LV is depolarizing), whereas the QRS in V6 is positive when the LV is depolarizing.

AXIS DEVIATIONS

The normal mean QRS axis is between –30° and +100°. > +100° is right axis deviation (RAD), whereas < –30° is left axis deviation (LAD). A quick, fairly accurate method to determine this is to just look at I and aVF. If both are prominent, you can quickly tell in which quadrant the mean vector lies. Visualize the following:

- Both (+) = Normal
- I (+) and aVF (–) = Check for LAD
- Both (–) = Extreme right or left axis
- I (–) and aVF (+) = Check for RAD

Left axis deviation (LAD) is usually due to left anterior hemiblock and, therefore, is a marker for CAD—as are all fascicular blocks.

Right axis deviation (RAD) is often a normal finding in children and young adults. Other causes include left posterior hemiblock (LPHB), RVH, and acute or chronic RV overload syndromes such as pulmonary hypertension/embolism, and pulmonic stenosis. If an adult is incidentally found to have RAD, do further workup.

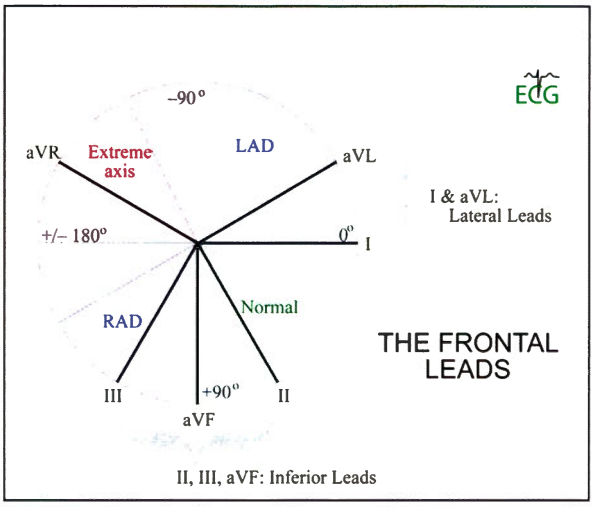


Figure 5-7: Axis Determination Diagram

RATES AND INTERVALS

The ECG is recorded on paper with a 1 mm² graph, with a thicker line every 5 mm. Because the paper moves at 25 mm/s, each thicker line is 1/5 of a second—or 0.2 sec (200 ms), and each mm represents 0.04 sec (40 ms). The interval covering 5 thicker lines (or "big squares") is 1 second.

There are a couple of quick ways to determine the heart rate. I'll discuss the RR interval, but any prominent wave of the standard QRS may be used to determine the interval. Using a calculator, a quick and accurate method for determining heart rate is 1,500/RR interval in mm. So, if the beat interval is 28 mm, the rate is 1,500/28 = 54 bpm. A less accurate, but easier, method is to divide 300 by the number of "big squares" in the RR interval. If the beat interval is 28 mm, this is not quite 6 big squares. You divide 300 by 6 and get 50, but you know the heart rate is actually a little faster because the interval is not quite 6 big squares. A derivative of this is the method taught in Dubin's book, *Rapid Interpretation of EKG's*, in which you memorize 2 sets of triplicates: 300–150–100 and 75–60–50. These match to the heart rates corresponding to RR intervals of 1, 2, 3, 4, 5, and 6 big squares.

Normal rate is 60–100 bpm. Sinus tachycardia is defined as a sinus rhythm of > 100 bpm; sinus bradycardia is < 60 bpm. So, an RR interval < 3 big squares indicates tachycardia; > 5 big squares indicates bradycardia.

Quick Quiz

- Know how to very quickly determine the axis of an ECG. Brand Figure 5-7 into your brain!
- What are the causes of left axis deviation?
- What are the causes of right axis deviation?
- Does RAD always warrant additional workup in an adult?
- Name the causes of prolonged QT intervals. Yes, all of them that are listed in the text!

INTERVALS

PR INTERVAL

The PR interval indicates the time between atrial and ventricular depolarization. Normal duration is 3–5 small squares (120–200 ms). Longer than 200 ms (1 big square) is the definition of 1° AV block.

Shorter than 120 ms (3 small squares) may indicate WPW (delta wave), junctional rhythm (with retrograde P wave—see next), or left atrial overload (widened P wave—see next).

QRS DURATION

QRS duration is usually < 100 ms (i.e., 1/2 a big square). QRS > 120 ms may be caused by bundle-branch block, ventricular beat/rhythm/ventricular pacemaker, drugs such as tricyclics, and WPW. 100–120 ms is often due to an incomplete BBB.

QT INTERVAL

The QT interval corrected for rate is normally 340–430 ms. $QT_c = QT/(RR)^{0.5}$; that is, the QT interval (in ms or sec) divided by a conversion factor that, although dimensionless, is derived from the square root of the beat interval in seconds. Again: The RR interval in this calculation must be in seconds. (Consider the difference in dividing by the square root of 0.7 vs. the square root of 700!) When scanning ECGs, a rule of thumb is: The QT interval normally is ~ 40% of the RR interval—do the calculation for QT_c if it appears shorter or longer.

With prolonged QT_c, there is a tendency to develop *torsades de pointes*.

Prolonged QT_c has many causes:

- Tricyclic overdose
- Hypocalcemia
- Hypomagnesemia
- Hypokalemia
- Starvation
- CNS insult
- Hypothermia
- Type Ia and III antiarrhythmics (Ia = quinidine, procainamide; III = amiodarone, sotalol)

More recently discovered causes of prolonged QT_c are:

- Non-sedating antihistamines such as astemizole and terfenadine (since pulled from the market)—their QT prolongation tendency can be increased by erythromycins, some "azoles" such as ketoconazole, and hepatic dysfunction.
- Drugs such as methadone, phenothiazines, amiodarone, sotalol.
- Liquid protein diet.

Short QT_c can be caused by hypercalcemia and digitalis.

WAVEFORMS AND SEGMENTS

P WAVE

The P wave results from the depolarization of the atrium. The normal P wave is < 2 mm in height and < 120 ms (3 small squares) in duration, and the normal axis is –50 to +60 degrees. (Where else have you seen 120 ms? The normal PR interval is 120–200 ms.) See Figure 5-8.

Most information from the P wave can be derived from II, aVR, and V1. As the wave of depolarization spreads from the SA node high in the right atrium and through the right and then left atrial myocardium, the mean vector is downward and to the patient's left—so the normal P wave is positive in II and negative in aVR.

A retrograde P wave is negative in II and positive in aVR—indicating an ectopic focus originating in the inferior part of the atrium or at the AV junction, resulting in a wave of depolarization traveling toward aVR (picture this!). A retrograde P wave from the AV junction often causes a tracing with a short PR interval.

Because atrial depolarization traverses from the patient's right to left, the left/initial side of the P wave represents the right atrium, while the right/terminal side of the P wave represents the left atrium (mid-P wave is both).

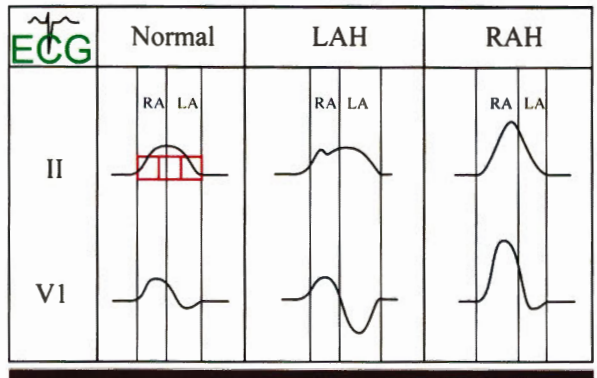


Figure 5-8: P wave in Atrial Enlargement

The normal P wave is positive in lead II and positive or biphasic in V1; when biphasic, the P wave is positive on the left side and a little negative on the right side. This is because the wave of depolarization through the atrium is toward V1 in the right atrium (left side of P wave) and somewhat away from V1 in the left atrium (right side of P wave).

With right atrial preponderance, (enlargement, hypertrophy, overload), the right atrial (initial) portion of the P wave is widened, and therefore overlaps onto the left atrial portion of the P wave. The P wave width stays normal (< 120 ms), but look for an increased P wave amplitude in II (also III and aVF, but just look at II) and in V1 (the positive portion). Actually, the P wave being "peaked" in II is more important than it being tall.

Decreased P wave amplitude is seen in severe hyperkalemia.

With left atrial overload, the right side of the P wave is enlarged, resulting in a wide P wave with a shortened or absent PR interval (i.e., < 120 ms). Other typical findings are a widened notched P wave in II and an enlargement of the negative portion of the P wave in V1. The most sensitive ECG finding for left atrial enlargement is a negative P wave in V1, with a duration of > 40 ms (1 small square). On the other hand, the most specific ECG finding is a notched P wave (usually in II) with an interpeak distance of > 40 ms.

COPD: Because of the hyperexpanded lungs, the heart assumes a more vertical position, and there is resultant RAD of the P wave. A +90° P wave axis is highly suggestive of COPD. The pulmonary hypertension may result in right atrial preponderance with associated P wave changes (see previous discussion).

T WAVE

The T wave is usually in the same direction as the QRS, indicating that repolarization is actually occurring in the opposite direction of depolarization.

Peaked T waves are sometimes associated with the following:

- Hyperkalemia
- Hyperacute MI
- Intracerebral hemorrhage
- In septal leads (V1-2) in evolving post-MI

Focal-flipped T waves may accompany:

- Ischemia
- V1-2 with RBBB, RVH, and RV HTN
- V1-2 with LVH
- Lateral leads (I, aVL, V6) with LBBB
- The precordial leads with LVH with "strain"

Diffuse flipped T waves may accompany:

- Pericarditis
- Diffuse ischemia; post-resuscitation
- Metabolic abnormality
- Intracerebral hemorrhage

U WAVE

The U wave occurs just after the T wave. It is usually small and is best seen in V2-3. If seen, it is usually a < 1 mm, rounded deflection in the same direction as the T wave. If the U wave is prominent, there is an increased tendency for *torsades de pointes*. Prominent U waves are present with hypokalemia, bradycardia, digitalis, and amiodarone.

Negative U waves are considered significant—even if the rest of the ECG is normal! Causes are ischemia, HTN, AV valve disease, and RVH. Negative U waves occur in up to 60% of patients with an anterior MI, up to 30% of patients with an inferior MI, and up to 30% of angina patients.

ST SEGMENT

There are 3 main causes of ST-segment elevation: acute MI, Prinzmetal angina, and pericarditis. It may also be present with early repolarization variant, intracerebral hemorrhage, hypertrophic cardiomyopathy, LVH, LBBB, cocaine abuse, myocarditis, and hypothermia.

ST-segment depression occurs with:

- Subendocardial ischemia (especially if downsloping or flat), such as seen in classic angina
- ST depression in V1-2 with an acute posterior MI
- Reciprocal depression in V1-2 with some inferior wall MIs—especially those with lateral or posterior extension

There may also be reciprocal ST depression in inferior leads with some anterior/septal MIs:

- LVH with LV strain (ST depression with flipped T waves in precordial leads)
- Isolated RV infarction, when there is ST elevation in V1 and ST depression in V2
- RVH that may cause RAD and ST-segment depression preceding a flipped T wave in V1
- Digitalis toxicity
- Hypokalemia

QRS COMPLEX

In QRS complex, depolarization of the ventricles occurs simultaneously after the depolarization of the interventricular septum. The normal mean vector of depolarization of the interventricular septum points from the patient's left to the right across the septum. You see this as a small initial deflection, which is positive in V1 (R wave) and negative in V6 (Q wave) (Figure 5-9).

Quick Quiz

- What are the P wave findings for RAH? For LAH?
- When are peaked T waves seen?
- When are focal flipped T waves seen?
- U waves indicate a predisposition to what serious condition?
- What is the significance of a negative U wave?
- What are the common causes of U waves?
- Name the 3 main causes of ST-segment elevation.
- What are the causes of ST-segment depression?
- What are the ECG criteria for LVH? RVH?

The left ventricle is normally much more massive than the right ventricle; therefore, the mean QRS vector (reflecting depolarization of the ventricles) is strongly to the patient's left. You see a large negative deflection in V1 and positive deflection in V6. On the frontal plane, as mentioned above, the mean vector is between –30 and +100 degrees.

The normal duration of the QRS is < 100 ms.

QRS changes seen with ventricular hypertrophy and conduction disturbances are discussed next.

VENTRICULAR HYPERTROPHY

LVH

LVH (left ventricular hypertrophy) causes a prolongation of activation of the myocardium. It is thought that relative coronary insufficiency (increased muscle mass > increase in size of the capillary bed) may be a factor in this prolonged activation. Another factor may be the overgrowth of the muscle mass relative to the Purkinje system.

This prolongation of activation, in addition to moving the mean QRS axis more posterior, superior, and to the left, also results in a reversal of repolarization, which now proceeds from the endocardium to epicardium, and is reflected by a flipped T wave in the septal leads (V1-2).

LVH causes an exaggeration of the negative deflection in V1 and the positive deflection in V6. There are several accepted ECG criteria for LVH, including: SV1 + (RV5 or RV6) > 35 mm or (RV5 or RV6) > 25–35 mm. This is read "the S in V1 + the R in V5 is > 35 mm," etc. (Figure 5-9).

The diagnosis of LVH is strengthened by an intrinsicoid deflection of > 50 ms (1.25 small squares). This is the time from the beginning of the QRS complex to the peak of the R wave. For greater ease of use, intrinsicoid deflection is often called the "R peak time." Note: When you notice an obvious intrinsicoid deflection, make sure to check the PR interval—you might be looking at a delta wave in WPW!

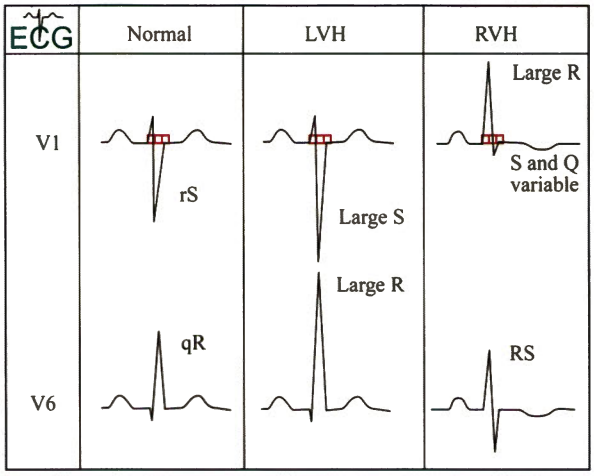


Figure 5-9: Ventricular Hypertrophy

Although the specificity of the various ECG criteria for LVH is quite high at ~ 95%, the sensitivity is low and varies from 25% for the above criteria to 50% for a complicated point system. Note that if the prevalence of LVH in a population is 5%, there will be many more false negatives and many more false positives than true positives, making this fairly useless as a screening test. [Go and work this out using the Bayesian 4-square! Population 10,000; sensitivity = 25%; specificity = 95%; find all the other numbers. Answer: TP = 125, FP = 475, FN = 375, TN = 9025; PPV = 21% (not good!); NPV = 96%. Statistics are covered in General Internal Medicine section, Book 5.]

When there is left axis deviation, the ECG criteria for LVH change! Use: SIII > 15 mm (Rosenbaum).

A left ventricular "strain" pattern may be present with LVH. LV strain is precordial ST-segment depression and flipped T waves seen in a patient with ECG criteria for LVH.

RVH

Because RVH (right ventricular hypertrophy) is such an abnormal condition, with the mass of the right ventricle increasing to the point of shifting the mean QRS vector to a right axis, the specificity for RVH is very high when ECG criteria are met—although, as with LVH criteria, the sensitivity is low.

ECG criteria for RVH are right axis deviation and, again, because of repolarization changes, ST-segment depression and a flipped T wave in V1, sometimes in V2. The ST-segment depression and flipped T wave generally indicate RV stress/hypertension (Figure 5-9).

Pulmonary Embolism (PE): Note that with acute, severe pulmonary embolism (acute cor pulmonale), ECG changes are reflective of acute RV strain with RV and RA dilation +/– ischemia. There is often a RBBB, sometimes RAD, and usually clockwise rotation. Because these are all nonspecific findings, and because of the changing nature of this event, the most important factors that increase sensitivity of the ECG in the setting of possible PE is a prior ECG tracing for comparison and serial tracings after admission. S1Q3T3 pattern (S wave in lead I, Q wave in lead III, and an inverted T wave in lead III) is an indication of RV strain and is a specific, but not sensitive, indication for acute PE.

CONDUCTION DISTURBANCES

AV BLOCKS

AtrioVentricular blocks are due to conduction disturbances at the AV node. Know the 3 degrees and their patterns.

1° AV block prolongs the PR interval by > 200 ms (1 big square).

2° AV block results in 2 main patterns:

- Mobitz I: Wenckebach phenomenon: progressive prolongation of the PR interval until there is a dropped QRS (ventricular beat).
- Mobitz II: Normal PR intervals, but periodically there is a dropped QRS. 2:1 AV block is 2 P waves for each QRS, 3:1 is # of P waves for each QRS, etc. Mobitz II almost always has a wide QRS complex (if narrow, usually Mobitz I).

3° AV block. No depolarizations are conducted through the AV node. The P wave and QRS have independent regular rhythms (AV dissociation). If the QRS complex has a normal width (< 100 ms), there is a junctional ectopic pacemaker. Junctional pacing rate is 40–60 bpm, whereas ventricular pacing is 20–40 bpm. Note: The AV node has no pacemaker activity. Junctional pacing originates from the myocardial tissue at the AV junction. (It may be near the AV node, but it is not a part of the AV node!)

BUNDLE-BRANCH BLOCK

Overview

Just a little after the AV node, the fast conduction pathway, known as the bundle of His, splits in two. These two fast conduction pathways travel down the interventricular septum, and one then goes to the right ventricle, while the other one—functionally if not anatomically—splits again and proceeds to the anterior and posterior sections of the left ventricle. If conduction in one of these pathways is blocked, the depolarization downstream to that pathway is delayed because the myocardial tissue in that area can then be depolarized only via the depolarization wave from much more slowly conducting adjacent myocardial tissue. Refer to Figure 5-10.

LBBB

Left bundle-branch block (LBBB): The QRS is prolonged with a duration of 120–180 ms (3–4.5 small squares). Because the left ventricle depolarization is now transmyocardial, it is depolarized over a longer period, resulting in an RR' (notched or slurred) in the lateral leads (I, aVL, and V6), and there is a corresponding SS' (also called QS) in V1. 1/2 of patients have a normal axis, 1/2 have LAD (–30° to –90°).

The T wave vector and sometimes the ST segment are opposite in direction to the mean QRS vector in LBBB. Therefore, as illustrated in Figure 5-10, you will see negative T waves following the positive RR' in I, aVL, and V6—and positive T waves following the negative QRS in V1-3.

Important note: In LBBB, the left side of the septum depends on myocardial conduction to depolarize; hence, conduction is slow over the left side and depolarization progresses from right to left, causing an rS or QS in V1. This right-to-left depolarization of the septum overcomes the expression of any septal Q waves with an MI—including the inferior leads. So, just as new septal Q waves will not appear in a patient with LBBB and an acute MI, also MI-related septal Q waves will disappear if LBBB develops because of the MI. So, LBBB makes it impossible to use the ECG as an evaluation tool in a patient you suspect of having an MI.

Criteria for LBBB:

- QRS = 120–180 ms (3–4.5 small squares).
- The left ventricle is depolarized, later resulting in an RR' (slurred or notched) in V6 and an SS' (QS) in V1.
- The T wave is often opposite the mean QRS vector in anteroseptal and lateral leads.

Incomplete LBBB fulfills the above criteria, except QRS < 120 ms.

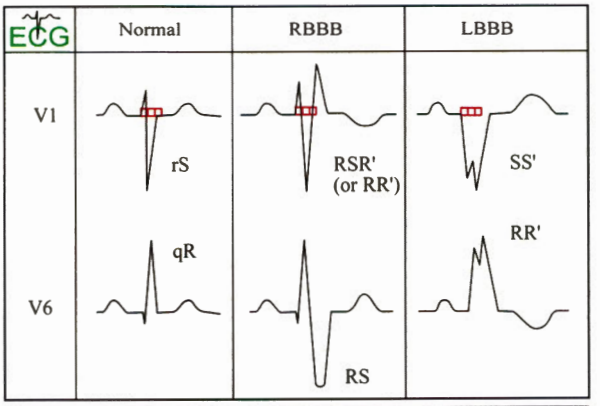


Figure 5-10: Bundle-Branch Block

Quick Quiz

- In LBBB, the left side of the septum depends on what to depolarize?
- What do you see on an ECG in LBBB? RBBB?
- What is so serious about a recent MI and the development of a bifascicular block?

RBBB

Right bundle-branch block (RBBB): The direction of septal depolarization is normal—left to right, but the right ventricle is depolarized over a longer period, resulting in an RR' or RSR' ("rabbit ears") in V1 and an S wave in V6. Visualize how the RSR' in V1 is formed: The initial R wave is due to normal left-to-right septal depolarization, the S is depolarization of the left ventricle, and the final R' is due to the delayed depolarization of the right ventricle. In V6, the S wave is due to delayed depolarization of the right ventricle.

The T wave is usually negative in V1, sometimes in V2.

Criteria for RBBB:

- QRS > 120 ms (3 small squares).
- Depolarization of the right ventricle is delayed, resulting in an RSR' ("rabbit ears") or RR' in V1 and often a slurred S wave in V5-6.
- Flipped T waves in V1, sometimes V2.

Incomplete RBBB fulfills the above criteria, except QRS < 120 ms.

LAFB

Left anterior fascicular block (LAFB) or left anterior hemiblock (LAHB). QRS duration is 100–120 ms. Septal activation is in a left-to-right (normal) and inferior direction. This inferior septal depolarization is sometimes reflected in a Q wave in the lateral leads (I and aVL). Because the last part of the heart to depolarize is the left posterobasal to anterolateral wall, the mean frontal QRS vector has a left-facing axis (–45° to 0°). This also causes lead I to record a large R wave and the inferior leads to record a large S wave. Left axis deviation (LAD) more negative than –45° with a normal QRS duration is nearly always due to LAFB. Actually, LAFB is the component that causes the LAD in 1/2 of patients with LBBB.

Criteria for LAFB:

- Left axis deviation (LAD) –45° to –90°, with a large S wave in the inferior leads (II, III, and aVF) and a dominant R wave in I
- Absence of other causes of LAD (incomplete or complete LBBB)
- Poor R wave progression across the precordium

LPFB

Left posterior fascicular block (LPFB) or left posterior hemiblock (LPHB): This problem is rare, and the ECG pattern is rather nonspecific because you can also see it in patients with RVH, lateral infarction, and emphysema. You can be sure that it is a LPFB only if it is a recent change—all else being the same. The septal depolarization is left to right but directed superiorly—causing a small Q wave in the inferior leads. Because final depolarization in the heart is in the inferior and posterior walls with the vector pointing inferior and to the right, there are large R waves in the inferior leads (II, III, aVF) and large abnormal S waves in the lateral limb leads (I, aVL). This also results in a mean QRS axis of +80° to +140°. The T wave is normal.

Criteria for LPFB:

- Small Q and large R (qR) waves in II, III, and aVF
- Small R wave in I, followed by a large S wave in I, aVL
- Rightward axis (+80° to +140°)

Bifascicular Block

Bifascicular block has 3 presentations:

1) Complete LBBB
2) RBBB + LAFB
3) RBBB + LPFB

The last is the least common. Anterior MI and calcific aortic stenosis are associated with bifascicular block. Remember that acute MI + a new bifascicular block indicate a high risk for progression to complete heart block.

WIDE QRS

Wide-complex QRS may be caused by BBB, ventricular origin of the complex, and/or aberrant conduction. More on this is discussed next and under the *previous* Arrhythmia topic on page 5-35.

ARRHYTHMIAS

ECTOPIC vs. PACEMAKER

An ectopic beat occurs from an ectopic (abnormal) focus earlier than the expected next beat. It may originate in the atria, AV junction, or the ventricle.

Throughout the heart are foci of cells with pacemaker capability, which can take over if there is a delay in depolarization, such as when the SA node ceases to function normally or there is a severe conduction disturbance. Atrial, non-SA node pacemaker activity has an inherent rate of 60–80 bpm. AV junction (not AV node!) pacemaker rate is 40–60 bpm. Ventricular pacemaker rate is 20–40 bpm (idioventricular rhythm).

Note that ectopic beats are different from escape/pacemaker beats. Ectopic beats are early. Escape beats are at the rate of inherent pacemaker activity.

ATRIAL ARRHYTHMIAS

Atrial fibrillation:

- No P waves: "irregularly irregular" rhythm
- Clinically: varying pulse pressure and no a waves

Atrial fibrillation is the result of multiple ectopic foci firing continuously or disorganized atrial activity. It is thought to be due to a micro-reentry mechanism. No P waves are seen, although there is loud, chaotic atrial "noise" throughout the tracing.

Atrial flutter (Type I):

- High atrial rate: characteristic rate ~ 300 bpm (range 240–340), usually with a 2:1 AV block
- Sawtooth formation
- Whole number ratio of flutter waves to QRS complexes

Atrial flutter is due to a wave of depolarization repeatedly going around and around the atrium—usually with an anatomic obstacle, such as an AV valve, in the pathway. This results in the "sawtooth"-appearing P wave with an atrial rate of ~ 300 bpm (but it varies between 240 and 340 bpm). There is usually a 2:1 or 3:1 AV block with a resulting ventricular rate of 150 or 100, respectively.

There is also a Type II atrial flutter with a much higher atrial rate: 340–440 bpm.

Wandering pacemaker is exactly what the name implies. The pacing impulse migrates from one atrial pacemaker focus to another. It is a benign condition seen mostly in young people—especially athletes. The varying focus is reflected by varying shapes of the P wave.

Multifocal atrial tachycardia (MAT) is similar to wandering pacemaker, except that MAT occurs at a higher rate with more chaotic switching between pacemakers. MAT is associated with COPD, hypoxia, digitalis, theophylline, severe hypokalemia, and hypomagnesemia. Atrial rate is 100–130 bpm. The rhythm is "irregularly irregular."

Sinus pauses result in a long TP interval. An ectopic escape beat (different P wave) may precede the resumption of the rhythm. If an atrial pacemaker takes over the rhythm, the rate is usually 60–80 bpm. If a junctional pacemaker focus takes over the rhythm, this is termed a "junctional (escape) rhythm." With a junctional rhythm, there is a change in the P wave—it may not be visible or it may be a retrograde P wave very close to the QRS (short PR interval). Junctional rate is normally 40–60 bpm.

VENTRICULAR ECTOPIC BEATS AND HEART BLOCK

Premature ventricular contraction (PVC):

- The QRS complex occurs earlier than expected (premature), is wider than normal, and has a higher amplitude than normal.
- P wave is obscured in the QRS complex.
- T wave is inverted.
- The next RR interval is longer than normal. This is called a full compensatory pause. The SA node is not reset by the ventricular depolarization—hence, the P waves march out normally.

A ventricular escape beat may occur if the sinus pause is long enough, and no atrial or junctional pacemakers kick in.

Complete (3rd degree) heart block has an atrial beat marching independently of a junctional or ventricular escape beat. Remember junctional = narrow, 40–60 bpm. Ventricular = wide, 20–40 bpm. Medication and certain illnesses can affect these rates.

Study tip: Now is a good time to review ventricular tachycardias vs. aberrant conduction. See the discussion on page 5-39.

MYOCARDIAL INFARCTION

COMMON FINDINGS

[Know this section!] Common findings in myocardial infarction: Within the first minute or so of acute ischemia, the T waves flip. After 1–2 minutes, they become positive and peaked (hyperacute). Then injury to the cells occurs, causing the ST segment to elevate. Q waves are associated with cell death. These associations of ECG changes with the actual pathophysiologic processes are somewhat artificial, but clinically useful.

Again:

1) T wave changes (ischemia), then
2) ST-segment changes (injury), and then
3) Development of Q waves (cell death)

LOCATION OF MI vs. ECG CHANGES

Left ventricle:

- Septal MI = changes in V1-2
- Anterior MI = V3-4
- Anteroseptal MI = V1-4
- Lateral MI = I, aVL, V5,V6
- Anterolateral = I, aVL, V3-6 (if V1-6 = extensive anterolateral MI)
- Inferior MI = II, III, aVF
- Apical MI = II, III, aVL and any of V1–V4
- Posterior MI = tall R in V1-2; ST depression in V1-2
- High lateral MI = I, aVL

QuickQuiz

- What is the difference between an ectopic beat and an escape beat?
- What are the ECG findings with atrial fibrillation?
- What are the ECG findings with MAT?
- What are the ECG findings with a PVC?
- Describe the sequence of ECG changes with the different phases of an MI.
- What ECG changes occur with a septal MI? Anterior? Lateral? Know all these!
- What conditions can cause diffuse inverted T waves?
- What conditions can cause a prolonged QT?
- What type of MI is AV node dysfunction associated with? What about bifascicular block?
- What conditions cause resting ST elevation?

Right ventricle:

- RV infarction is best determined by placement of the right precordial leads. ST elevation in V4R to V6R is fairly sensitive and specific for RV infarction (~ 90% each). It is diagnostic of RV infarction if the ST elevation is greater in V4R than in V1-3.
- With the standard ECG, suspect an RV infarction if, with an inferior infarction, there is also ST-segment elevation in V1-2. Also be suspicious in the instance where you see ST-segment elevation in V1, along with ST-segment depression in V2!

NOTES

With acute inferior MI, there may be reciprocal ST depression in septal leads (V1-2). With an anterior/septal MI, there may be reciprocal ST depression in the inferior leads.

The trick for reading the ECG with a suspected acute posterior MI is to hold the ECG upside-down and backwards, while holding it up to a light to see the tracing. Study V1-2. A posterior MI assumes the morphology of other MIs with this trick. (R waves look like Q waves and ST depression appears to be ST elevation.)

Posterior MI is often associated with inferior- and lateral-wall MIs. So, if you see either of these, look closely for signs of a posterior MI.

Signs of acute infarct and ischemia signs may be obscured by LBBB, WPW, HOCM, and ventricular pacemakers.

REMEMBER ...

These ECG changes [know!]:

- Diffuse, inverted T waves: ischemia, pericarditis, drugs, metabolic abnormality, and CNS insult (intracerebral hemorrhage).
- Prolonged QT: drug effect (quinidine, sotalol, dofetilide), hypocalcemia, hypomagnesemia, and CNS insult. This is a precursor to *torsades de pointes*.
- Peaked T waves: hyperkalemia. (If severe, ECG looks like a sine wave.)
- Large U waves are associated with hypokalemia, bradycardia, and digitalis toxicity.
- A low-voltage ECG tracing is associated with pericardial effusion, hypothyroidism, obesity, and COPD.
- AV node dysfunction is associated with an inferior MI and with digitalis and verapamil toxicity.
- Bifascicular block, in contrast, is associated more with anteroseptal MI and calcific aortic stenosis.
- What causes ST-segment elevation during a stress test? Stress-induced coronary artery spasms.
- What causes resting ST elevation?
  - Acute MI
  - Post-MI wall motion abnormalities in the infarcted areas
  - Spontaneous spasm of the coronary artery
  - Pericarditis

ANALYSIS

Analyzing the ECG:

First, check the rate and rhythm. Next, check the intervals—especially the PR, QRS, and QT. Then, check waveforms.

The ECGs on the following pages will give you a little practice.

Figure 5-11 provides a memory aid for ECG interpretation. This memory aid is copied below each ECG on the following pages.

Table 5-12 and Table 5-13 summarize the information in the ECG section of the text.

Study tip:

To the top left of each ECG is the presenting information. The bottom-left notes are the main findings. So don't look at the bottom information until you have done your reading of the ECG!

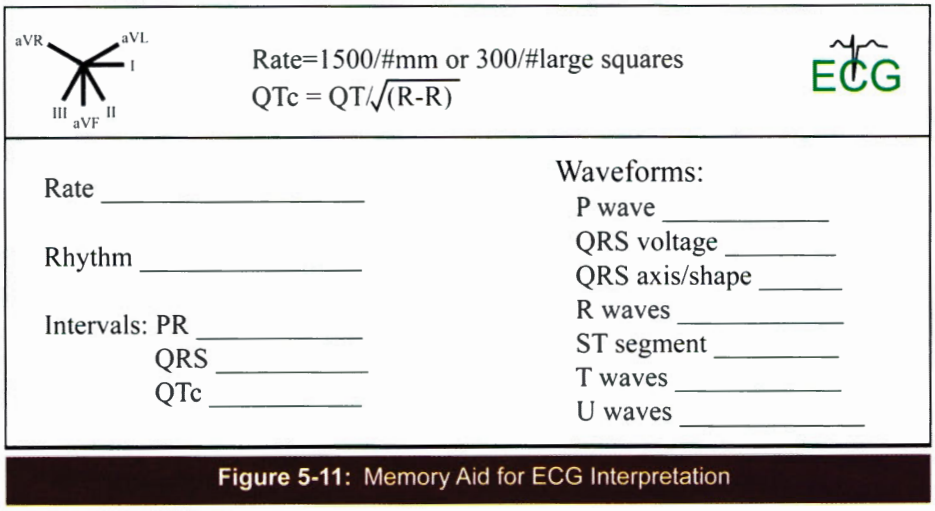


Figure 5-11: Memory Aid for ECG Interpretation

Table 5-12: ECG Summary Table (1 of 2)

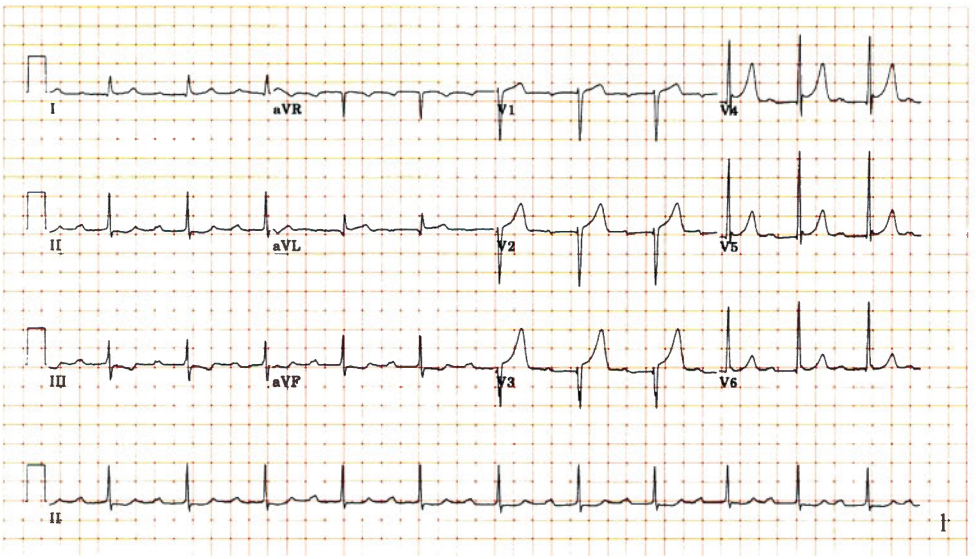
		Normal	Abnormal	Common Causes
Heart Rate	1) HR	60–100 bpm	< 60 bpm	Sinus bradycardia, sick sinus syndrome, beta-blockers, junctional or ventricular rhythm
			> 100 bpm	Sinus tach, A-fib with rapid V response, V-tach, SVT
Heart Rhythm	2) Rhythm	NSR	Many	Multiple (see text)
Intervals and Durations	3) PR	120–200 ms	< 120 ms	Shorter than 120 ms (3 small squares) may indicate: WPW (delta wave) Junctional rhythm (with retrograde P wave) Left atrial overload
			> 200 ms	First degree AV block
	4) QRS	< 100 ms	> 100 ms	Think WPW if the PR interval is shortened Ventricular ectopy or pacemaker Aberrant conduction (BBB) Drugs; tricyclic overdose (also causes long QT)
	5) QTc	340–430 ms	> 440 ms	Hypocalcemia lengthens ST segment Hypokalemia (often w/large U waves) Type Ia (quinidine) and III (amiodarone) antiarrhythmics Tricyclic overdose (also causes long QRS) Intracranial bleed (also causes inverted Ts)
			< 340 ms	Hypercalemia. Digitalis effects (which also often causes a scooping of the ST segment)

Table 5-13: ECG Summary Table (2 of 2)

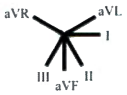
Waves and Segments	Abnormal	Common Causes
6) P wave	> 2 mm, > 120 ms	Tall, peaked P waves in II suggest right atrial overload Biphasic in V1 and broad and notched in II suggest left atrial overload
	Decreased	Severe hyperkalemia
7) Q waves	In ant or inf leads	Acute: More severe MI
8) QRS voltage	High	LVH (SV1 + RV5 > 35 or RV6 > 25–35)
	Low	1) Pericardial effusion 2) Tamponade 3) Emphysema 4) Obesity 5) Amyloid
9) QRS axis	Right: > +110 Left: < –30;	Right axis may be seen in: 1) Normal in children and young adults 2) LPFP (+80 to +140) 3) RVH 4) RV overload (pul HTN, PE) Left axis may be seen in: LAFB and LBBB
10) R wave		1) Intrinsicoid deflection > 50 ms with some LVH 2) Delta wave with WPW; V1 shows RR' or RSR' with RBBB 3) Large R in I with LBBB and LAFB 4) Large R in inferior leads with LPFB 5) R in V1, V2 with posterior MI
11) S wave		1) S wave in V6 with RBBB 2) Large S waves in inferior leads with LAFB 3) Large abnormal S waves in lateral leads (I, aVL) with LPFB
12) ST segment	Elevation	1) Diffuse: acute pericarditis or myocarditis 2) Localized means MI, transmural ischemia, or wall motion disorder: Area involved: 1) Septal = changes in V1-2 2) Anterior MI = V3-4 3) Anteroseptal MI = V1-4 4) Anterolateral = I, aVL, V3-6 (if V1-6 also, then = extensive anterolateral MI) 5) Lateral MI = I, aVL, V6 6) Inferior MI = II, III, aVF 7) Posterior MI = tall R in V1-2
	Depression	1) Subendocardial ischemia (esp if downsloping or flat) such as seen in classic angina 2) ST depression V1-2 with acute posterior MI 3) Reciprocal depression V1-2 with some inferior wall MIs—esp. those w/lateral posterior extension; Also, conversely, reciprocal ST depression in INFERIOR leads with some ANTERIOR MIs 4) Dig toxicity 5) LVH 6) hypokalemia 7) LV strain (ST depression with flipped T waves)
13) T wave	Tall, peaked	1) Hyperacute MI (usually with ST elevation and sometimes Q waves) These are followed in time by a more prolonged T wave inversion 2) Hyperkalemia (early sign—followed in time by widened QRS and decr. P wave, prolonged QRS, and AV conduction problems) 3) Intracerebral hemorrhage 4) Common in V1-2 with evolving posterior MI
	Inverted	1) Post hyperacute MI (see above) 2) Severe ischemia (may have prolonged QT) 3) Post resuscitation 4) Pericarditis 5) Intracranial bleed can cause deep inverted T waves (along with prolonged QT) 6) In lateral leads (I, aVL, V6) with LBBB 7) In septal leads (V1-2) with RBBB and LVH 8) In V1 with some RVH (suggests RV hypertension)
14) U wave	> 1 mm, positive (nl)	1) Indicates increased susceptibility to *torsades de pointes* 2) Drugs: Type Ia (usu w/prolonged QT) 3) Hypokalemia: (usu w/prolonged QT)
	Negative	1) HTN 2) AV valve disease 3) Major ischemia 4) RVH 5) Up to 60% of patients with an anterior MI 6) Up to 30% of patients with an inferior MI 7) Up to 30% of angina patients

ECG

Case 1: A 57-year-old man with previous myocardial infarction and chronic hypertension on digoxin, beta blockers, and ACEI.



Note first degree AV block with P-R of 340 ms. Left ventricular hypertrophy. Probable early repolarization—the sharp S wave in V4-5 enhances the likehood of the ST segment being due to repolarization. Possible inferior ischemia.



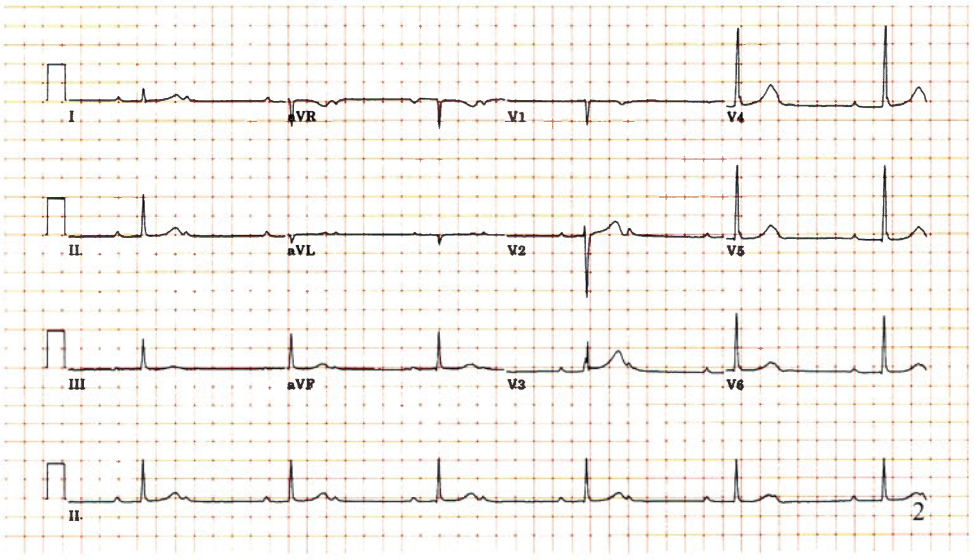
Rate _____

Rhythm _____

Intervals: PR _____
QRS _____
QTc _____

Waveforms:
P wave _____
QRS voltage _____
QRS axis/shape _____
R waves _____
ST segment _____
T waves _____
U waves _____

Case 2: A 36-year-old man with history of cocaine abuse and "slow heart rate" since his teens.



Note sinus rhythm with Mobitz type I second degree 2:1 AV block. This initially looks like Mobitz II, but there is a subtle increase in the PR interval and this also has a narrow QRS complex (Mobitz II usually has a wide complex)

Rate _____

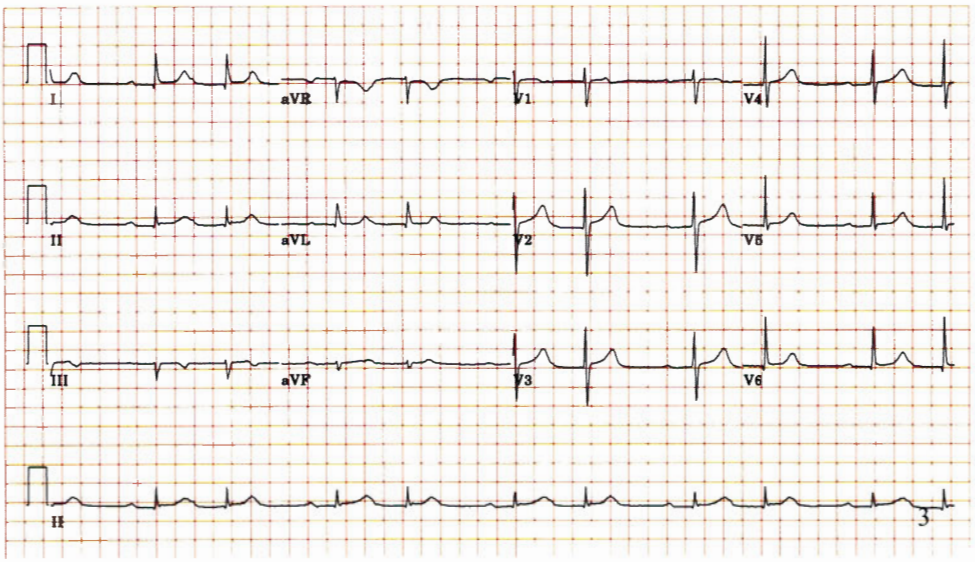
Rhythm _____

Intervals: PR _____
QRS _____
QTc _____

Waveforms:
P wave _____
QRS voltage _____
QRS axis/shape _____
R waves _____
ST segment _____
T waves _____
U waves _____

ECG

Case 3: A 76-year-old man with chronic heart failure.



Rate _____

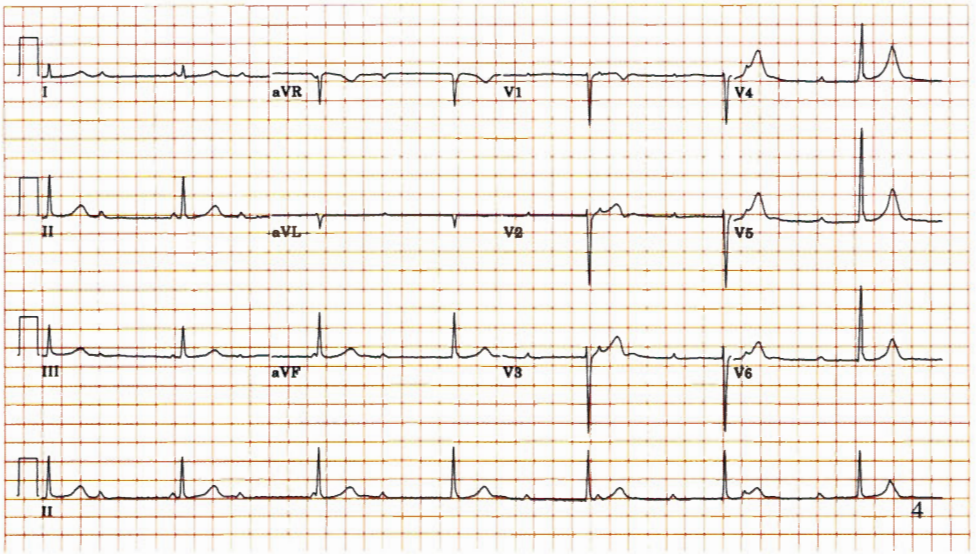
Rhythm _____

Intervals: PR _____
QRS _____
QTc _____

Waveforms:
P wave _____
QRS voltage _____
QRS axis/shape _____
R waves _____
ST segment _____
T waves _____
U waves _____

Note second degree Mobitz type I (Wenckebach) 3:2 AV block. The first P wave is visible, the second is just peeking out of the previous T wave, and the third is fused with the previous T wave. Possible COPD.

Case 4: A 36-year-old man with history of drug abuse and "slow heart rate" since he was young.



Rate _____

Rhythm _____

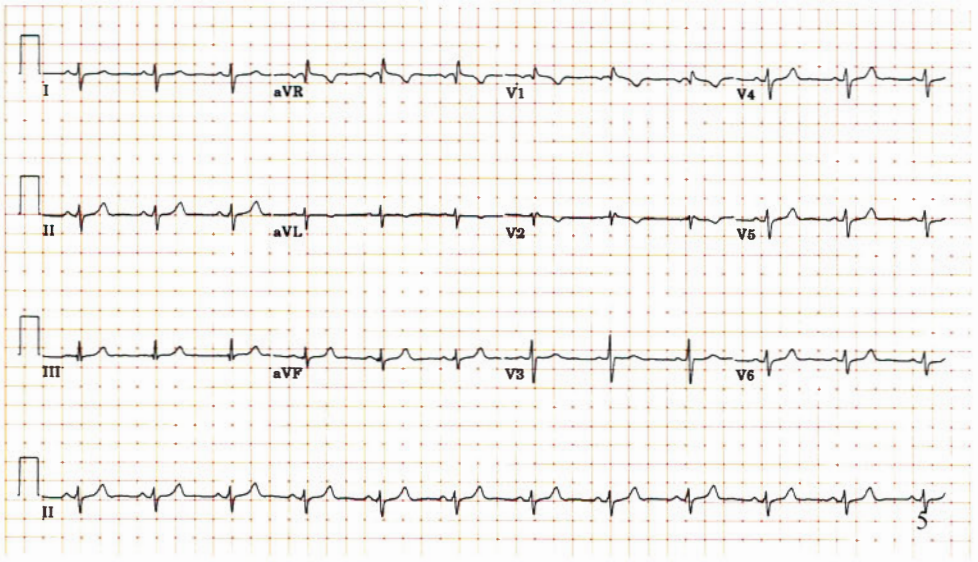
Intervals: PR _____
QRS _____
QTc _____

Waveforms:
P wave _____
QRS voltage _____
QRS axis/shape _____
R waves _____
ST segment _____
T waves _____
U waves _____

Note sinus rhythm with complete/ third degree AV block.

ECG

Case 5: A 54-year-old woman with history of chronic smoking.



Rate _____

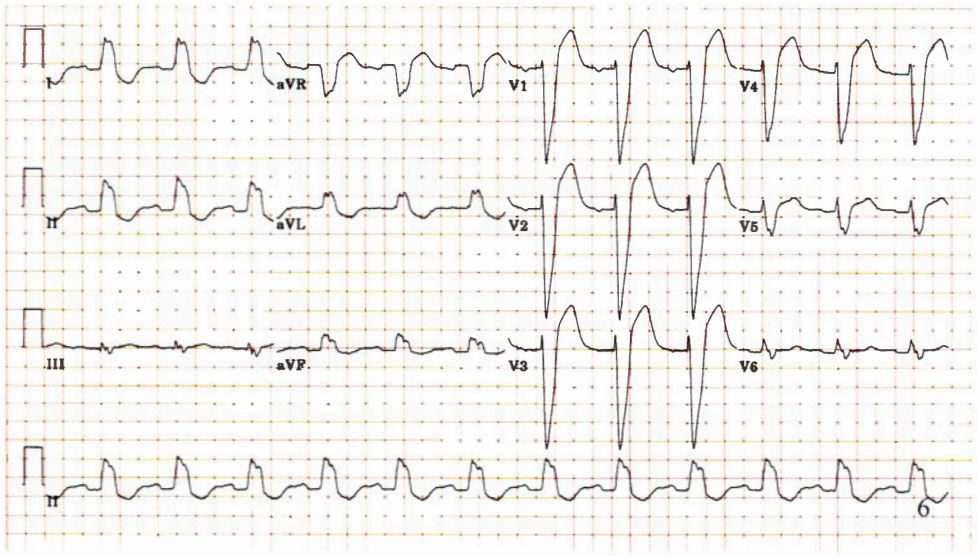
Rhythm _____

Intervals: PR _____
QRS _____
QTc _____

Waveforms:
P wave _____
QRS voltage _____
QRS axis/shape _____
R waves _____
ST segment _____
T waves _____
U waves _____

Note sinus rhythm with right axis deviation and incomplete RBBB consistent with pulmonary disease pattern.

Case 6: A 77-year-old man with a history of chronic congestive heart failure.



Rate _____

Rhythm _____

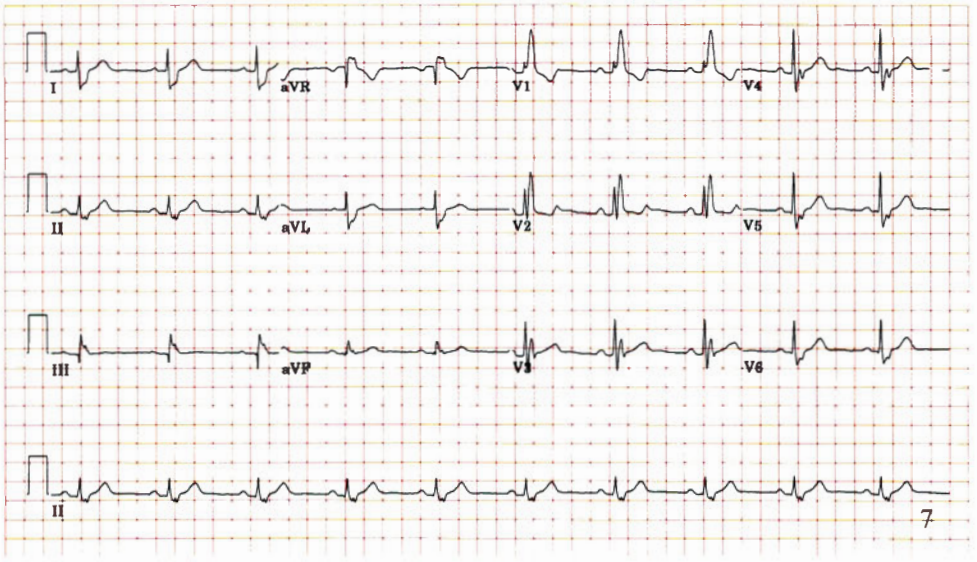
Intervals: PR _____
QRS _____
QTc _____

Waveforms:
P wave _____
QRS voltage _____
QRS axis/shape _____
R waves _____
ST segment _____
T waves _____
U waves _____

Note sinus rhythm with complete LBBB (bifascicular block) and left atrial enlargement. This LBBB is a little atypical, but notice the large slurred S in the anteroseptal leads and the T wave opposite the mean QRS in the anterolateral leads. Also notice the terminal portion of the QRS in V1-3 is slurred—also consistent with LBBB.

ECG

Case 7: A 67-year-old man with a history of a cardiac murmur.



Rate _____

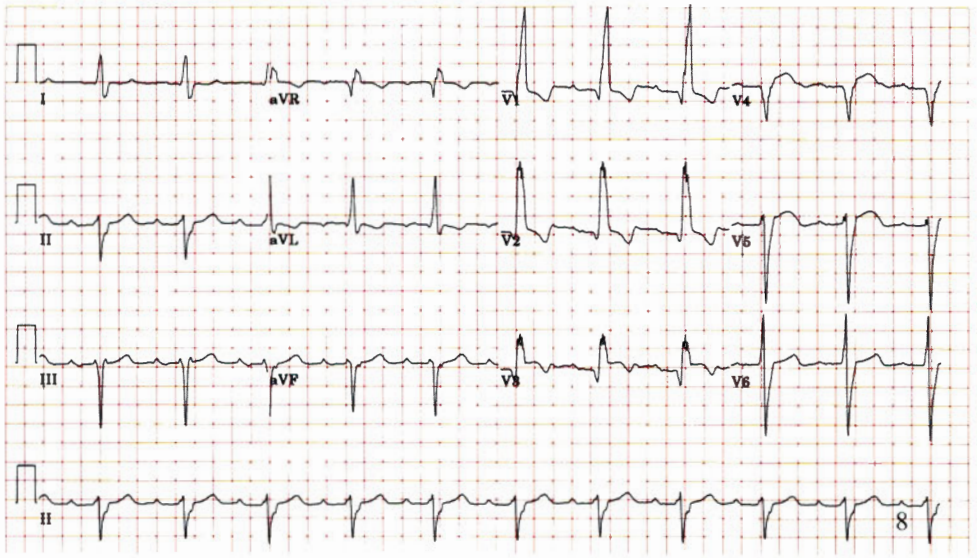
Rhythm _____

Intervals: PR _____
QRS _____
QTc _____

Waveforms:
P wave _____
QRS voltage _____
QRS axis/shape _____
R waves _____
ST segment _____
T waves _____
U waves _____

Note sinus rhythm with RBBB.

Case 8: A 77-year-old man with a history of myocardial infarction and recurrent syncope.



Rate _____

Rhythm _____

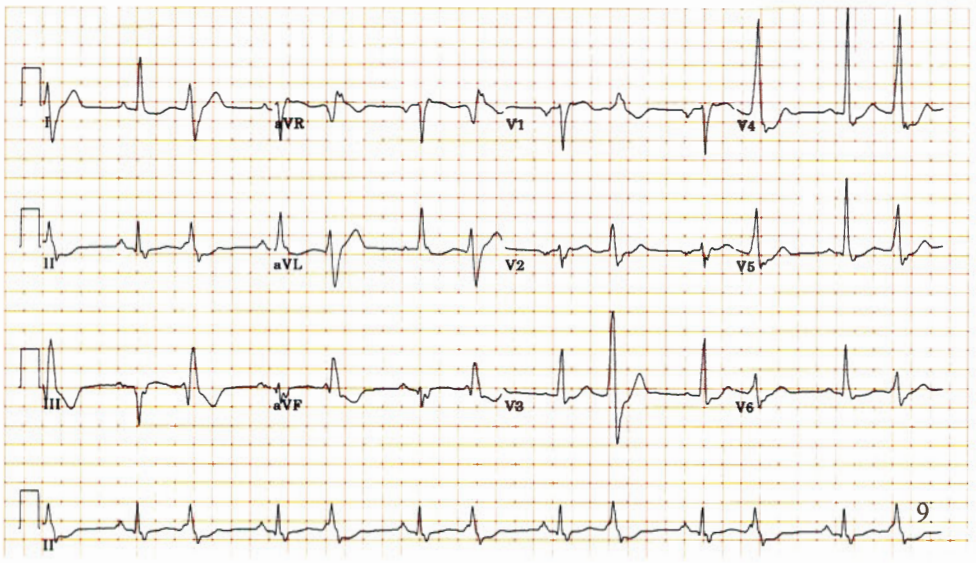
Intervals: PR _____
QRS _____
QTc _____

Waveforms:
P wave _____
QRS voltage _____
QRS axis/shape _____
R waves _____
ST segment _____
T waves _____
U waves _____

Note sinus rhythm, first degree AV block, RBBB and left anterior fascicular block (bifascicular block). Note also Q waves from V1 to V4 consistent with anteroseptal infarct.

ECG

Case 9: A 65-year-old man with recurrent palpitations.



Rate _____

Rhythm _____

Intervals: PR _____
QRS _____
QTc _____

Waveforms:
P wave _____
QRS voltage _____
QRS axis/shape _____
R waves _____
ST segment _____
T waves _____
U waves _____

Note sinus rhythm with frequent ventricular premature beats in bigeminy. Note the full compensatory pause after the PVC.

Case 10: A 45-year-old man with a history of rheumatic fever as a child and cardiac murmurs.

Rate _____

Rhythm _____

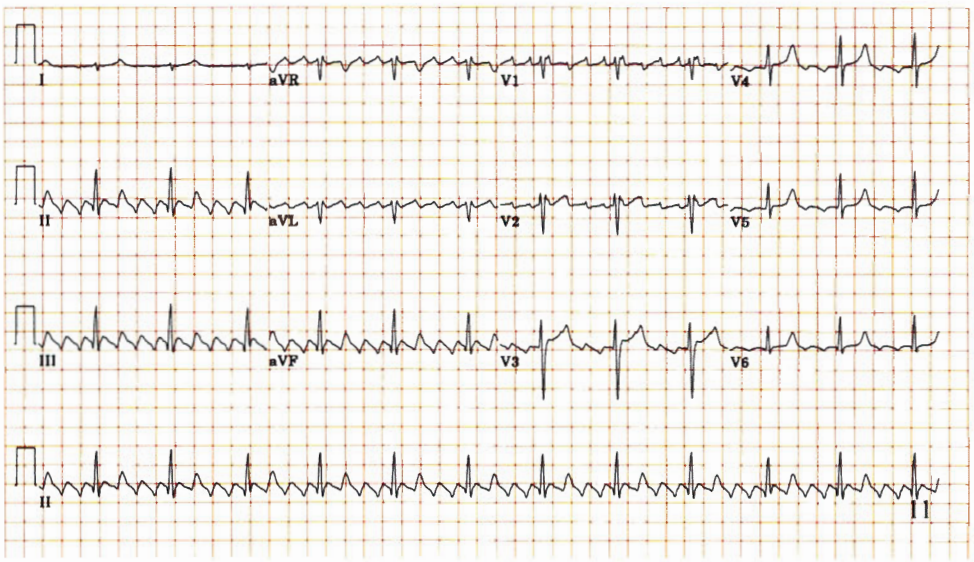
Intervals: PR _____
QRS _____
QTc _____

Waveforms:
P wave _____
QRS voltage _____
QRS axis/shape _____
R waves _____
ST segment _____
T waves _____
U waves _____

Note atrial fibrillation and flipped T's in the inferior-lateral leads.

ECG

Case 11: A 44-year-old man with a history of 2-pack-per-day smoking for 15 years.



Rate _____

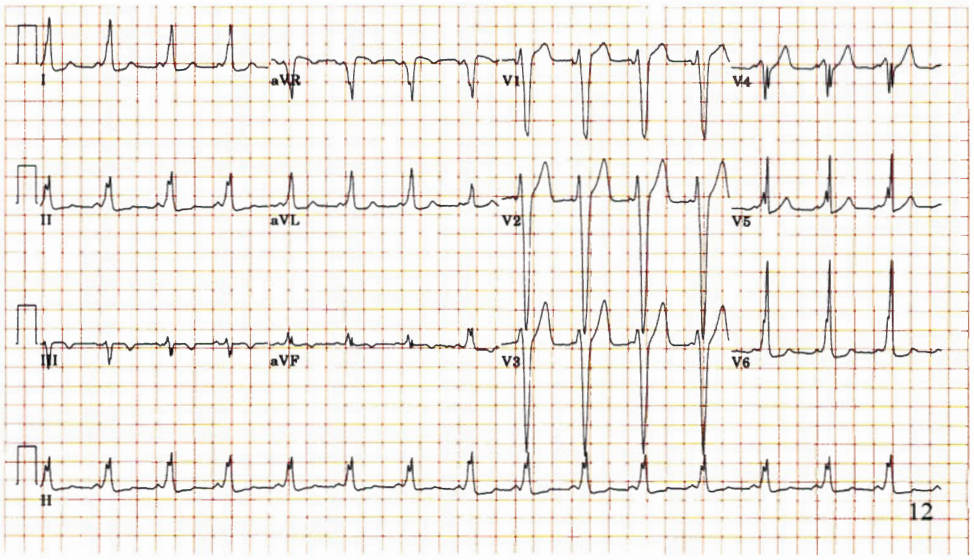
Rhythm _____

Intervals: PR _____
QRS _____
QTc _____

Waveforms:
P wave _____
QRS voltage _____
QRS axis/shape _____
R waves _____
ST segment _____
T waves _____
U waves _____

Note atrial flutter with 4:1 block, vertical axis, and incomplete RBBB.

Case 12: A 34-year-old man with history of palpitations since childhood.



Note sinus rhythm, short P-R interval, and delta wave consistent with Wolff-Parkinson-White syndrome. This is one of those ECGs on which you may mistake the delta wave for prolonged intrinsicoid deflection (as seen with LBBB and LVH) until you check the PR interval and find it is short!

Rate _____

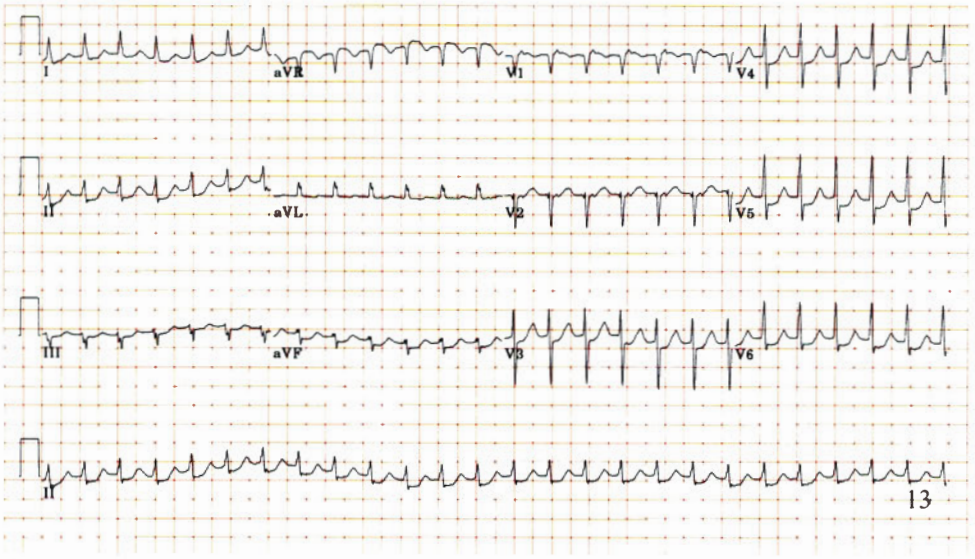
Rhythm _____

Intervals: PR _____
QRS _____
QTc _____

Waveforms:
P wave _____
QRS voltage _____
QRS axis/shape _____
R waves _____
ST segment _____
T waves _____
U waves _____

ECG

Case 13: A 74-year-old woman with recent episodes of light headedness and palpitations.



Note narrow QRS tachycardia with retrograde P waves evident in precordial leads V1 and V2 consistent with AV node reentrant tachycardia at a rate of approximately 150 bpm. Also pronounced ST-segment depression in the inferio-lateral leads—it is likely that the rapid rate is a factor in the ischemia.

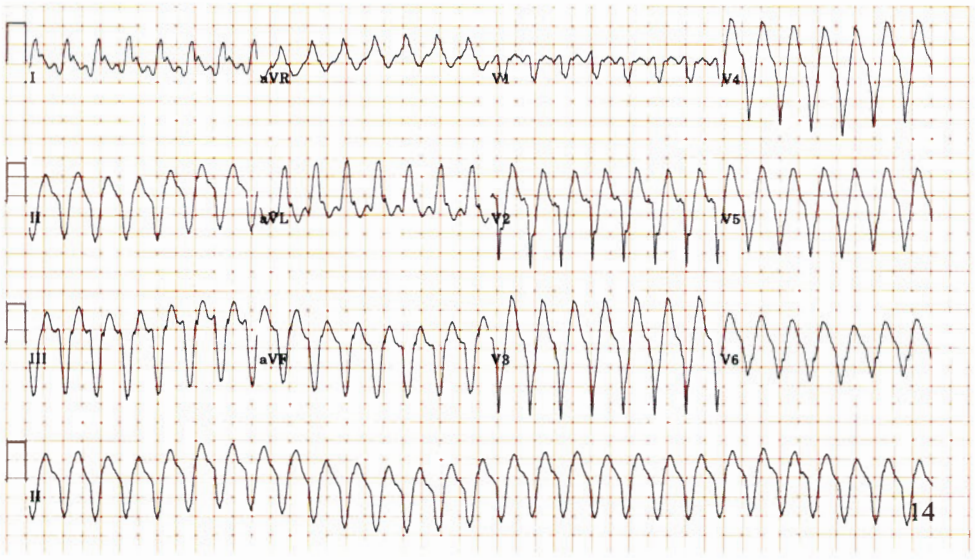
Rate _____

Rhythm _____

Intervals: PR _____
QRS _____
QTc _____

Waveforms:
P wave _____
QRS voltage _____
QRS axis/shape _____
R waves _____
ST segment _____
T waves _____
U waves _____

Case 14: A 71-year-old man with history of previous myocardial infarction and coronary artery bypass surgery admitted for chest pains and syncope.



Note the wide QRS tachycardia with negative concordance in the precordial leads consistent with ventricular tachycardia. Negative concordance is the QS pattern throughout the precordial leads; there is no hint of R wave progression.

Rate _____

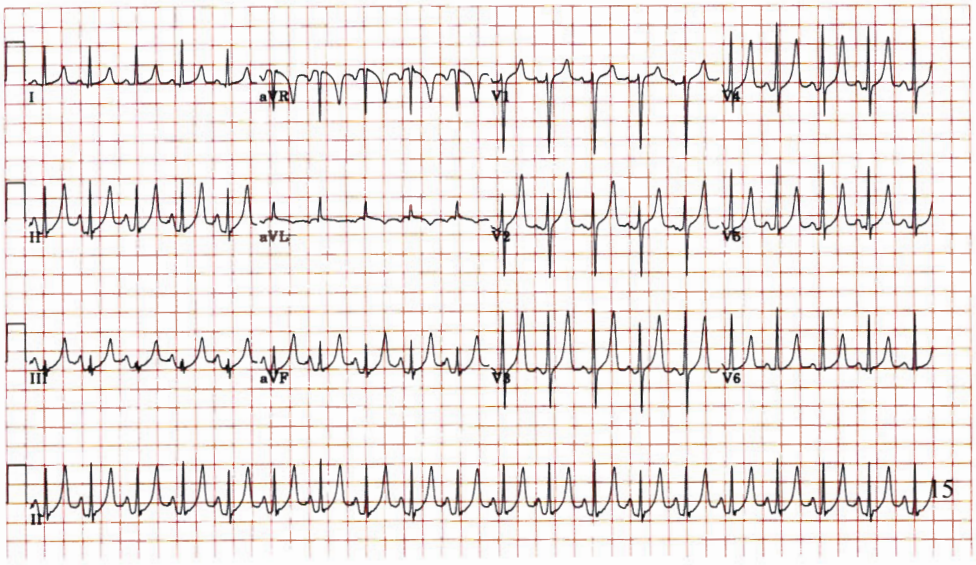
Rhythm _____

Intervals: PR _____
QRS _____
QTc _____

Waveforms:
P wave _____
QRS voltage _____
QRS axis/shape _____
R waves _____
ST segment _____
T waves _____
U waves _____

ECG

Case 15: A 47-year-old man with Type I diabetes and chronic renal insufficiency admitted with diabetic ketoacidosis and serum potassium of 7.



Rate _____

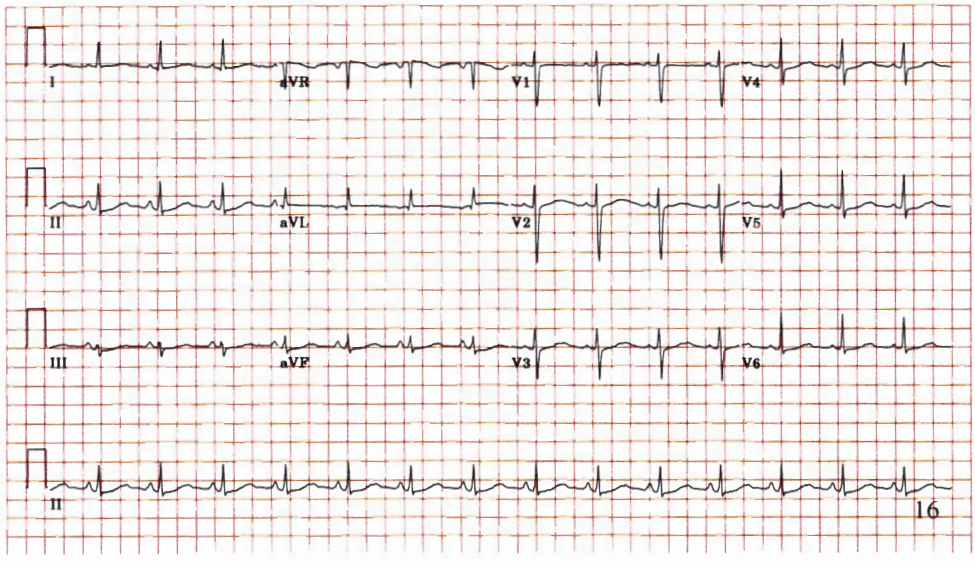
Rhythm _____

Intervals: PR _____
QRS _____
QTc _____

Waveforms:
P wave _____
QRS voltage _____
QRS axis/shape _____
R waves _____
ST segment _____
T waves _____
U waves _____

Note tall and peaked T waves.
LVH by voltage criteria.

Case 16: A 39-year-old woman successfully resuscitated from ventricular fibrillation with no evidence of acute myocardial infarction.



Rate _____

Rhythm _____

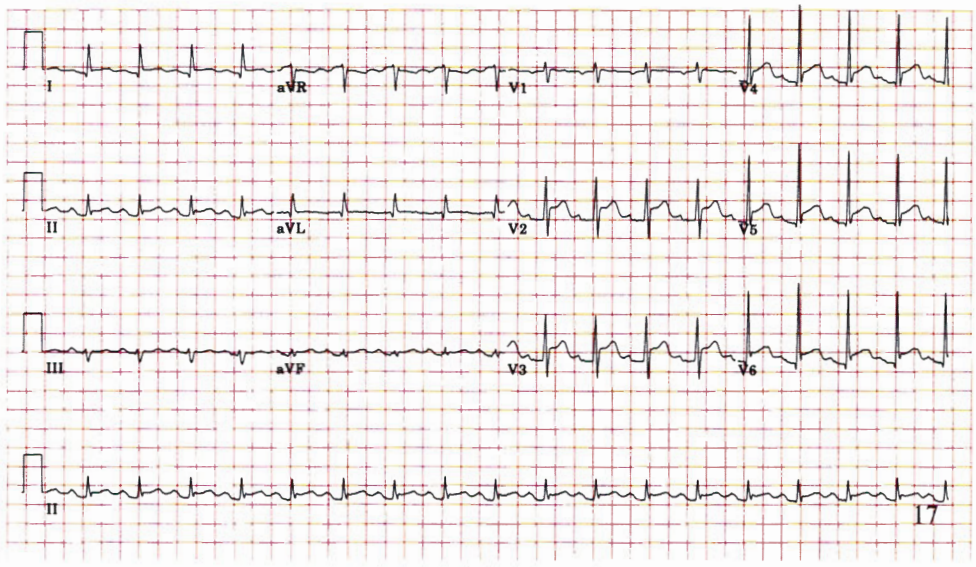
Intervals: PR _____
QRS _____
QTc _____

Waveforms:
P wave _____
QRS voltage _____
QRS axis/shape _____
R waves _____
ST segment _____
T waves _____
U waves _____

Note prolonged QT of 530 and a QTc of 640 ms. When measuring the QT interval, you must look at all the leads and choose the longest QT interval—in this case, use lead V2.

ECG

Case 17: A 65-year-old man admitted for pleuritic chest pains 1 week following a bout of flu-like symptoms.



Rate _____

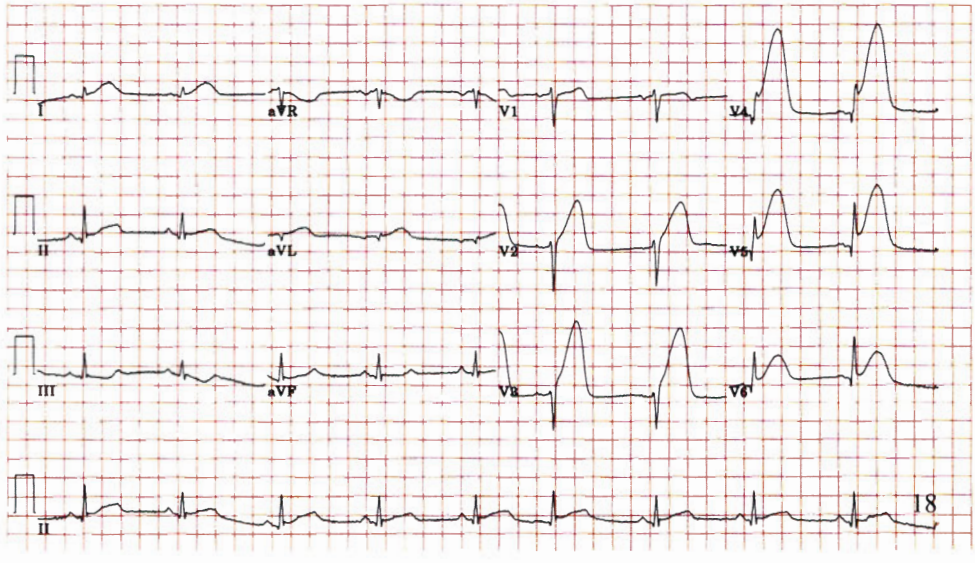
Rhythm _____

Intervals: PR _____
QRS _____
QTc _____

Waveforms:
P wave _____
QRS voltage _____
QRS axis/shape _____
R waves _____
ST segment _____
T waves _____
U waves _____

Note diffuse ST segment elevations consistent with pericarditis. There is PR segment depression best seen in II also often seen with pericarditis. Also note the concave ***up*** ST segment elevation more consistent with pericarditis than MI.

Case 18: A 65-year-old man admitted with a 2-hour episode of severe retrosternal chest pains and shortness of breath.



Rate _____

Rhythm _____

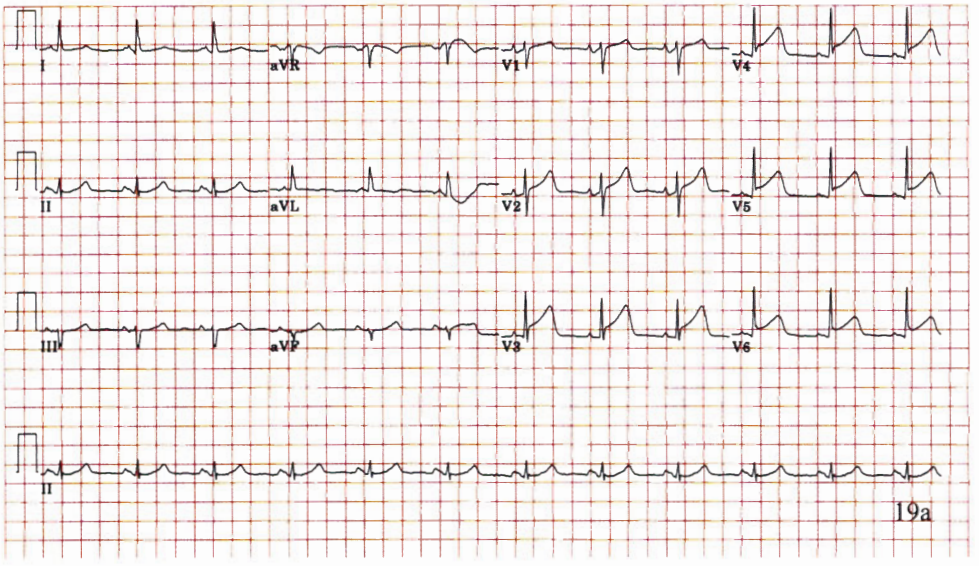
Intervals: PR _____
QRS _____
QTc _____

Waveforms:
P wave _____
QRS voltage _____
QRS axis/shape _____
R waves _____
ST segment _____
T waves _____
U waves _____

Note marked ST segment elevation in precordial leads consistent with acute extensive anterolateral infarction. Associated T waves are hyperacute.

ECG

Case 19a: An 80-year-old woman is seen in the emergency room 3 hours after waking up with severe retrosternal pressure and lightheadedness.



Note ST segment elevations in the precordial leads consistent with acute anterior wall infarction. Even though the ST segment is mildly concave up, the lack of an S wave in V4-5 makes early repolarization unlikely—as does the presenting complaint!

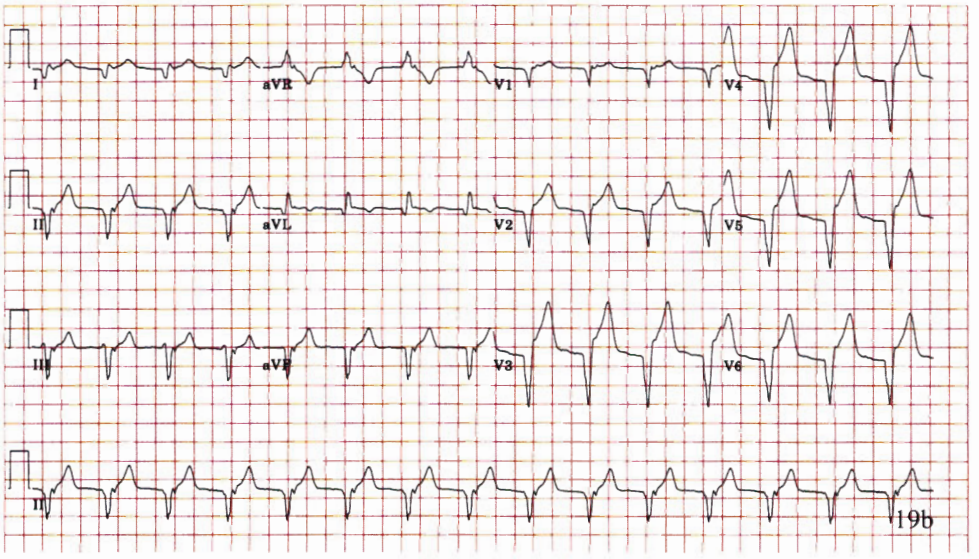
Rate _____

Rhythm _____

Intervals: PR _____
QRS _____
QTc _____

Waveforms:
P wave _____
QRS voltage _____
QRS axis/shape _____
R waves _____
ST segment _____
T waves _____
U waves _____

Case 19b: 20 minutes following infusion of a thrombolytic, a repeat ECG is performed.



Shows accelerated idioventricular rhythm (reperfusion arrhythmia) or "slow" ventricular tachycardia at 90 bpm. Note change in QRS duration and axis shift with retrograde P waves—showing a V-A association (i.e., the ventricle is resetting the atrium!).

Rate _____

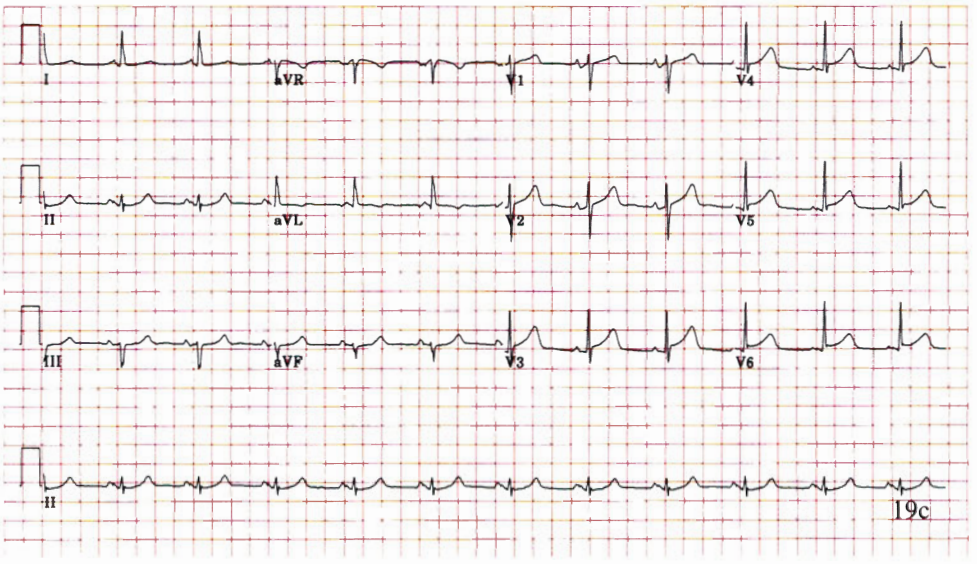
Rhythm _____

Intervals: PR _____
QRS _____
QTc _____

Waveforms:
P wave _____
QRS voltage _____
QRS axis/shape _____
R waves _____
ST segment _____
T waves _____
U waves _____

ECG

Case 19c: 90 minutes after thrombolysis the patient is pain free.



Rate _____

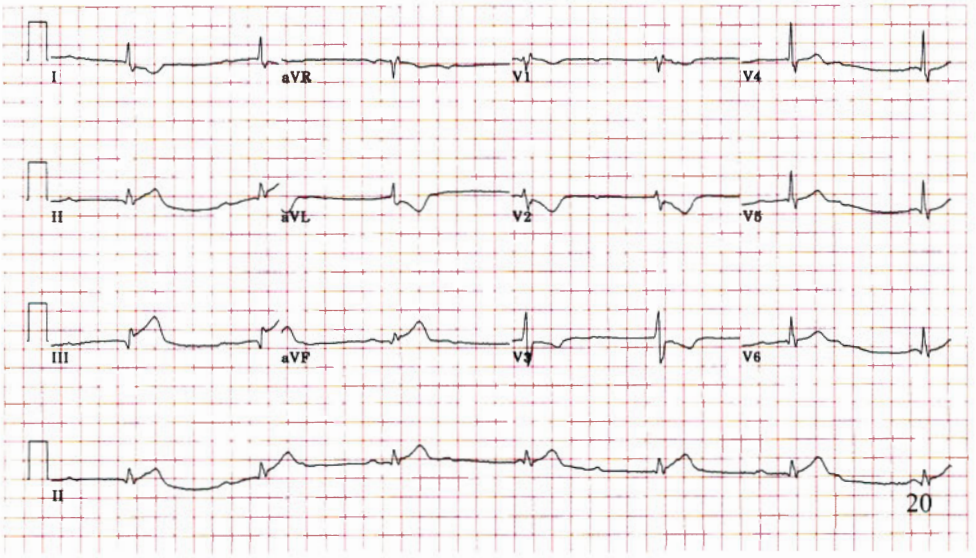
Rhythm _____

Intervals: PR _____
QRS _____
QTc _____

Waveforms:
P wave _____
QRS voltage _____
QRS axis/shape _____
R waves _____
ST segment _____
T waves _____
U waves _____

A repeat ECG shows significant resolution of the precordial ST segment elevations.

Case 20: A 65-year-old man with severe epigastric pains, nausea, and vomiting of 2 hours duration.



Rate _____

Rhythm _____

Intervals: PR _____
QRS _____
QTc _____

Waveforms:
P wave _____
QRS voltage _____
QRS axis/shape _____
R waves _____
ST segment _____
T waves _____
U waves _____

Note acute inferior infarction with reciprocal ST-segment changes in the right precordial leads and complete AV block shown by AV dissociation with an atrial rate of 75 and a ventricular rate of 40.

FOR FURTHER READING

PROCEDURES, LABS, PHYSICAL EXAM

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ECG Wave-Maven. http://ecg.bidmc.harvard.edu/maven/mavenmain.asp

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CORE CURRICULUM

15th EDITION

Robert A. Hannaman, MD
with Candace L. Walkley, MD

RHEUMATOLOGY

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Table of Contents

Rheumatology

LABS

OVERVIEW

Know everything covered in this topic area about Labs! If this is your first time through the Rheumatology section, go over this topic several times before you continue. What you learn here will enable you to make better sense of lab references later in this section.

Remember: No single blood test makes any rheumatologic diagnosis—and the ANA test is sometimes positive in many non-rheumatologic diseases.

Tests that are very specific are useful for "ruling in" the disease, and tests that are very sensitive are useful for "ruling out" the disease.

ANTINUCLEAR ANTIBODIES (ANA)

ANA Test

Antinuclear antibodies (ANA) are autoimmune antibodies that attack components of the nucleus. They are found in many autoimmune disorders. The most common ANA tests:

- Indirect immunofluorescence (IF)
- Enzyme-linked immunosorbent assay (ELISA).

IF is more sensitive; ELISA is less expensive.

Results are reported as titers (e.g., 1:320), with a particular pattern when positive.

Titers show the dilution at which the antibodies become undetectable. It is shown in doublings: 1:80, 1:160, 1:320, 1:640, etc.—so, the higher the number, the more antibodies in the serum.

Patterns are determined by looking at a specially prepared (fluorescent stain) slide that shows where the antibodies attack the nucleus. There are 6 different patterns: centromere, rim, speckled, diffuse, homogenous, and nucleolar. The rim pattern is very specific for systemic lupus erythematosus (SLE). The centromere pattern is specific for systemic sclerosis and limited scleroderma (previously CREST); it is also specific for primary biliary cirrhosis. The rest are of little value.

The ANA test is nonspecific and determines the overall titers of all the ANA patterns. Because the general population has low levels of ANAs, the test is not considered positive unless the titer is > 1:80. Some rheumatologic diseases that are ANA+:

- Drug-induced lupus (100%)
- SLE (93–100 %)
- Mixed connective tissue disease (MCTD) (93–100%)
- Limited scleroderma (previously CREST) and diffuse systemic sclerosis (60–90%)
- Sjögren syndrome (48–70%)
- Polymyositis/dermatomyositis (60%)
- Rheumatoid arthritis (RA; 40%)

Example of ruling in vs. ruling out: The ANA is positive in almost all patients with SLE (high sensitivity) but also is positive in many other diseases (low specificity). So, a negative ANA test is helpful for ruling out SLE, but a positive test is poor for ruling it in.

The patterns found with fluorescent staining differ with the various types of ANAs that attack different components of the nucleus. These different ANA attack points in the nucleus cause different diseases. We now have tests (below) that identify these antibodies far more precisely than the fluorescent staining.

When the ANA is positive and you suspect a specific rheumatologic disease, order the more specific antibody subtypes (ANA profile). Know which diseases are also associated with specific subtypes (Table 6-1). Again, the general ANA test is not specific enough to diagnose any disease, only to rule one out.

Specific ANA Tests

Anti-dsDNA (in high titer) and anti-Smith (anti-Sm) are very specific for SLE, so if one or both of these are strongly positive, the diagnosis of SLE is strongly supported. However, patients taking anti-TNF drugs (e.g., infliximab, adalimumab) can develop a lupus-like syndrome, as well as antibodies to anti-dsDNA (hence, they will be ANA positive also).

Anti-U1-RNP is very sensitive for MCTD but not very specific. In general, absence of the antibody excludes MCTD. Anti-U1-RNP and anti-dsDNA are often seen together because they bind to related antigens.

Antihistone antibody is seen in SLE and drug-induced lupus, but the SLE patients usually have other ANA subtypes also.

The antihistone antibody test is very sensitive for drug-induced lupus which is typically caused by procainamide, hydralazine, chlorpromazine, or quinidine. In general, absence of the antibody rules out drug-induced lupus in patients who are not on anti-TNF agents.

Why the exceptions with anti-TNF treatment? Because patients on anti-TNF treatment can develop (rarely) an antihistone negative severe lupus-like syndrome. Note that patients on anti-TNF treatment frequently develop ANA and anti-dsDNA positivity. See Biologic Agents on page 6-11.

But antihistone antibody can also be used to rule in drug-induced lupus. It is very specific for drug-induced

Table 6-1: Antinuclear Antibody Disease Associations

Antibody	Subclass	Associated With:
Specific ANAs	anti-dsDNA	Specific for SLE; an indicator of disease activity (as are complement levels) and identifies SLE patients with potential for significant renal disease. Absent in classic drug-induced SLE; sometimes develops in patients treated with TNF inhibitors.
	anti-Sm	Specific for SLE. Often seen with U1-RNP.
	SSA (Ro)	SLE, neonatal SLE, Sjögren's, and sometimes myositis. Usually not found in scleroderma; passively transferred from mother to baby → neonatal heart block. DR3 is associated with SSA.
	SSB (La)	SLE and Sjögren's; sometimes found in patients with +SSA. Also passively transferred from mother to baby → neonatal heart block.
	anti-U1-RNP	Specific for MCTD; also found in SLE—usually in association with anti-Sm.
	anti-histone	Drug-induced lupus and SLE. Mainly used to rule out drug-induced lupus caused by procainamide, hydralazine, chlorpromazine, and quinidine.
	anti-centromere	Limited scleroderma; identifies increased incidence of pulmonary arterial hypertension and improved survival.
	anti-topoisomerase I (anti-Scl-70)	Diffuse scleroderma; identifies increased incidence of interstitial lung disease and reduced survival.
	anti-synthetases	Anti-Jo-1 = type of anti-synthetase antibody; associated with myositis; identifies increased incidence of interstitial lung disease.

lupus—but only when the patient has a high pretest probability (e.g., history of use of procainamide) and does not test positive for other autoantibodies. Again, other antibodies along with antihistone antibody suggests SLE.

Anti-Scl-70 is specific for diffuse scleroderma; it is present in ~ 75% of cases. Its presence supports a diagnosis of systemic sclerosis and is associated with progressive skin involvement, pulmonary fibrosis, and a higher mortality.

Before going further, let's clarify the terms Ro and La. Anti-Ro (or just "Ro") was the term given for the specific ANA antibody causing the "speckled" ANA pattern found mainly in SLE and Sjögren syndrome. During the same period, a serum antibody was discovered in these patients, which was named anti-SSA (or SSA). These 2 antibodies turned out to be one-and-the-same antibody. So, these terms can be used interchangeably—you commonly see them together; e.g., Ro/SSA, SSA (Ro). Similarly, SSB is identical to La and commonly seen as La/SSB or SSB (La). Okay, let's move on.

ANCA

Anti-neutrophil cytoplasmic antibodies (ANCAs) are, as the term indicates, autoimmune antibodies against antigens in the cytoplasm of neutrophils. These are different from the anti-nuclear antibodies just discussed. ANCAs are markers for vasculitis, including drug-induced vasculitis (Table 6-2).

It is thought that the vasculitis may be caused by the ANCA antibodies, which stimulate the release of lytic enzymes from neutrophils.

Table 6-2: ANCAs

IF ANCA	ELISA	Disease
c-ANCA	anti-PR3+	Granulomatosis with polyangiitis
p-ANCA	anti-MPO+	Pauci-immune glomerulonephritis Churg-Strauss vasculitis Microscopic polyangiitis w/kidney involvement Anti-glomerular basement membrane antibody
	anti-MPO–	Crohn disease Ulcerative colitis Chronic active hepatitis Primary sclerosing cholangitis Primary biliary sclerosis Polyarteritis nodosa Chronic arthritides Normal controls Drug-induced ANCA-associated vasculitis

QuickQuiz

- What two ANA subtypes are specific for a diagnosis of systemic lupus?
- Anti-U1-RNP is a very sensitive indicator for what rheumatologic disorder?
- Which antibody is associated with drug-induced lupus?
- Which rheumatologic disease is associated with a positive c-ANCA and anti-PR3?
- Name 2 diseases that are p-ANCA+.
- Name 2 diseases that consume complement during a flare.
- What antibody test is more specific than rheumatoid factor for rheumatoid arthritis?

Two ANCAs are identified from their immunofluorescence (IF) pattern:

- c-ANCA: Antibodies are diffuse in the cytoplasm.
- p-ANCA: Antibodies are perinuclear.

These ANCAs can then be subdivided based on the antigen they are directed against: anti-proteinase 3 (anti-PR3; PR3 ANCA) or anti-myeloperoxidase (anti-MPO; MPO ANCA). Labs determine these antigens using an enzyme-linked immunosorbent assay (ELISA). This further analysis of the ANCA helps you narrow down a diagnosis.

So again, we have 2 ANCAs (c-ANCA and p-ANCA) that are further categorized, based on ELISA, into whether or not antibodies are directed against the PR3 or MPO antigens. (Proteinase 3 and myeloperoxidase are enzymes located in a neutrophil's alpha granules.)

• c-ANCA	• p-ANCA
• anti-PR3	• anti-MPO

The 2 on the left (c-ANCA and anti-PR3) are strongly related while the 2 on the right (p-ANCA and anti-MPO) are more loosely related. PR3 antigens usually cause the diffuse pattern seen in c-ANCA+ IF tests.

The combination of c-ANCA+ and anti-PR3+ is very specific for disease due to granulomatosis with angiitis (GPA; previously Wegener granulomatosis).

p-ANCA is less helpful because this IF pattern is nonspecific. Table 6-2 shows you that many diseases are p-ANCA+ (especially in the anti-MPO category). Any p-ANCA+ results should be further tested by ELISA for anti-MPO antibodies.

If anti-MPO+, especially think of Churg-Strauss, polyarteritis nodosa (PAN), idiopathic rapidly progressive glomerulonephritis (RPGN), and drug-induced ANCA-associated vasculitis (vasculitis, not lupus).

The most common causes of anti-MPO+ drug-induced ANCA-associated vasculitis are the anti-thyroid drugs propylthiouracil (PTU) and methimazole. Many other drugs are much less commonly associated.

So, one more time:

- c-ANCA+ plus anti-PR3+, think GPA (previously Wegener's)
- p-ANCA+ plus anti-MPO+, think Churg-Strauss, PAN, or RPGN

The sensitivity and specificity of these antibody tests are, in general, not high enough for them to be used for screening. Pretest probability of the disease in question is important and should be considered before ordering ANCAs.

COMPLEMENT

In rheumatologic diseases, hypocomplementemia is seen in SLE and vasculitis (rheumatoid and others).

There is more on the complement pathway in the Allergy & Immunology section, Book 4. But note: Complement components can be decreased due to a genetic deficiency, because either they have been consumed during complement activation, or they are being underproduced—as in eclampsia or HELLP syndrome (hemolysis, elevated liver enzymes, low platelets).

Know:

- **C3** is consumed with any activation of the complement pathway (classical or alternative).
- **C4** is consumed only with activation of the classical pathway (as with SLE).
- **CH50** assay measures total hemolytic complement of the classical pathway and requires all components (C1–C9) of the classical pathway for a normal result.

The CH50 assay is most useful when looking for a terminal complement deficiency (C5–C9), such as in patients with severe gonococcal infection. C3 and C4 are primarily used to follow disease activity in SLE.

RHEUMATOID FACTOR AND ANTI-CCP

Rheumatoid factor (RF) is positive in 80–85% of patients with RA, but it is not specific.

Anti-citrullinated cyclic peptide (anti-CCP antibody), a more recent discovery, appears earlier and has greater specificity (~ 97%) for the diagnosis of RA. RF and anti-CCP antibodies are associated with more aggressive RA and extraarticular manifestations.

HUMAN LEUKOCYTE ANTIGENS (HLA)

Overview

There are 2 main classes of HLA antigens:

- Class I includes the HLA-A, HLA-B, and HLA-C antigens.
- Class II includes the HLA-D antigens; e.g., DR2, DR3, and DR4.

HLA-B27

Know when HLA-B27 is found:

- Reactive arthritis (prev. Reiter syndrome): 60–80%; higher when sacroiliitis is present.
- Ankylosing spondylitis (AS): 90%.
- Psoriatic spondylitis: up to 60%.
- Inflammatory bowel disease (IBD) with associated central joint arthritis: up to 60%. But there is no HLA-B27 association when only peripheral joint disease is present in IBD patients.

Keep in mind that 7–8% of the healthy Caucasian North American population carries this haplotype; therefore, an individual with HLA-B27 has only a 10–20% risk of developing a related disease. Consequently, this test is of limited clinical usefulness. A negative result on the HLA-B27 test is useful in ruling out ankylosing spondylitis. See Table 6-3.

HLA-DR2, 3, 4

DR2 and DR3 are associated more often with SLE. DR3 is occasionally found in Sjögren disease and polymyositis. DR4 antigens are associated with severe RA. More in the Allergy & Immunology section, Book 4.

Table 6-3: Incidence of HLA-B27

Ankylosing spondylitis	90%
Reactive arthritis	60–80%
Yersinia, *Shigella*, and *Salmonella* arthropathy	80%
Uveitis	50%
Normal population	7–8%
Rheumatoid arthritis, Osteoarthritis, Rubella arthritis	10%

Although it does not cause reactive arthritis, *Klebsiella pneumoniae* has an enzyme (not encoded) that cross-reacts with the HLA-B27 test.

ERYTHROCYTE SEDIMENTATION RATE (ESR) AND C-REACTIVE PROTEIN (CRP)

The ESR and CRP are the most common acute phase reactants (APRs; inflammatory markers) used in clinical medicine. They are most helpful in determining disease activity and response to therapy. Unfortunately, they are of limited diagnostic utility since they are sensitive markers of inflammation but not specific for any particular disease. Diagnostically, they are most helpful to rule out inflammatory disease, especially when the pretest likelihood is low to moderate. Take note that an extreme elevation of the ESR (> 100 mm/hr) is almost always a hallmark of serious underlying disease, most commonly malignancy, infection, or inflammatory disorders (especially temporal arteritis).

THE JOINT

Synovium and its fluid: Type A cells of the synovial membrane are phagocytic, whereas type B cells probably synthesize hyaluronic acid. Chondrocytes make the cartilage. Cartilage is avascular and depends on the synovial fluid for nutrients. The chondrocytes can produce only a limited amount of collagen, so only slight damage is repairable.

The cell count in aspirated joint fluid decreases rapidly—so analyze it immediately. See Table 6-4.

Joint fluid is categorized based on the inflammatory response (WBC/mm^3):

- 0–200 = Normal
- 200–2,000 = "Noninflammatory" (osteoarthritis [OA], trauma, neuropathic joints, hypertrophic osteoarthropathy; occasionally SLE, scleroderma, and rheumatic fever)
- 2,000–50,000 = "Inflammatory" (RA, gout, pseudogout, SLE, scleroderma, reactive arthritis, ankylosing spondylitis, inflammatory bowel disease [IBD]-associated arthritis, infection)
- 50,000–100,000 with ≥ 75% neutrophils = Sepsis usually but occasionally crystalline disease (gout, pseudogout) can cause a count this elevated. Important exception—*Neisseria* gonococcal sepsis can have a synovial WBC count as low as 10,000.
- Hemorrhagic = trauma, bleeding diathesis, tumor, pigmented villonodular synovitis (PVNS)

Look for crystals in inflammatory fluid using the polarizing microscope. Look for uric acid crystals (gout) and calcium pyrophosphate dihydrate (CPPD) crystals (pseudogout). Both types have 2 colors: blue and yellow; hence, they are termed "birefringent." The crystals are identified, however, by the color of the crystals that are parallel to the microscope's color compensator.

QuickQuiz

- Compare and contrast "normal," "noninflammatory," "inflammatory," and "septic" joint fluid. (See Table 6-4.)
- Describe gout crystals.
- Describe CPPD crystals.

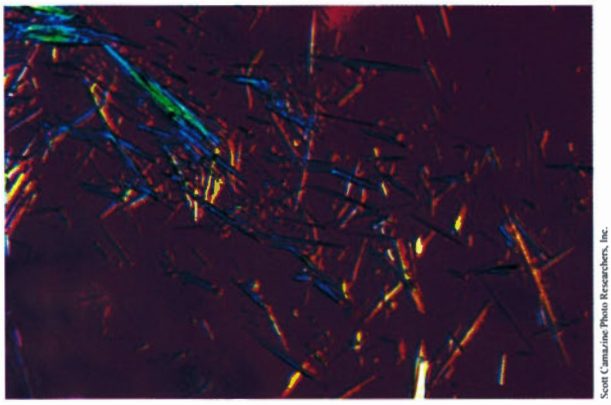
(Crystals perpendicular to the color compensator will be the opposite color.) Be concerned only about the crystal color that is parallel! If the crystals are yellow when parallel to the compensator, they are termed "negatively birefringent," and when they are blue, they are "positively birefringent."

Uric acid (gout) crystals are yellow when parallel to the compensator (negatively birefringent), and they are needle-like.

CPPD (pseudogout) crystals are blue (positively birefringent) short thick rods.

CPPD crystals attract neutrophils and can cause a purulent joint (with the high WBC count mentioned above in aspirated fluid). To be very certain that the crystals are actually causing the inflammatory reaction in the joint, you must see "intracellular crystals," which are crystals within the neutrophils, as opposed to crystals just floating around freely in the joint space. Important: Crystalline and infectious arthritis can coexist, so it is important to always send studies for both.

Again, you cannot simply look at a photo of a crystal and see whether it is positively or negatively birefringent;



Scott Camazine Photo Researchers, Inc.

Image 6-1: Birefringent crystals

you must know the direction of the compensator dial. For instance, in Image 6-1, you see needle-like crystals (so probably uric acid), but you won't know they are negatively birefringent unless the compensator is vertical and the vertical crystals are yellow.

Weight-bearing knee films are the initial diagnostic tests of choice for nontraumatic knee disorders (RA or OA) because weight bearing allows a more realistic evaluation of the joint space. If necessary, MRI can visualize all the components, except for normal synovium (too thin). The characteristic MRI signal described in some synovial diseases, such as PVNS, is very helpful for diagnosis.

GENETIC COLLAGEN DISORDERS

The inherited disorders of collagen encompass several different diseases, many of which cause hypermobility—e.g., Marfan syndrome, Ehlers-Danlos syndrome (EDS),

Table 6-4: Synovial Fluid Analysis

Joint Fluid	WBC (cells/mm³)	Other Findings	Disease Associations
Normal	0–200	None RBC	Normal or OA Internal derangement
Noninflammatory	200–2,000	None RBC	OA Internal derangement, TB, PVNS
Inflammatory	2,000–50,000	None Intracellular, strongly negatively birefringent crystals (yellow) Intraceullar, weakly positively birefringent crystals (blue) RBC	Inflammatory arthropathy (e.g., RA) Monosodium urate gout Calcium pyrophosphate deposition disease TB or fungal infection
Septic	50,000–100,000	None Intracellular, strongly negatively birefringent crystals Intraceullar, weakly positively birefringent crystals Organisms on Gram stain	Very inflamed inflammatory arthopathy (e.g., RA) Monosodium urate gout Calcium pyrophosphate deposition disease Bacterial infection

and homocystinuria. Defects in elastic fiber formation (Marfan syndrome) or in type II collagen (Stickler syndrome) are well defined at this time; different proteins are responsible for these syndromes. The following are the ones to remember.

Marfan syndrome:

- Long limbs (outstretched arms length > height)
- Pectus excavatum (sternum dips inward), or pectus carinatum (sternum protrudes outward)
- Aortic aneurysm/dissection
- Ectopia lentis (lenses displaced upward)
- Heart valve disease

Ehlers-Danlos syndrome: variable skin hyperelasticity and joint hypermobility. Several classifications:

- Classic type (old Types I and II) = includes most severe form (easily scarred skin and hypermobile joints)
- Hypermobility type (old Type III) = manifestations predominantly joint, not skin
- Vascular type (old Type IV) = manifestations predominantly skin, not joint, and predilection for rupture of large vessels
- Several other rarer types

Osteogenesis imperfecta (OI): Defects in procollagen genes cause the variants, but all have:

- osteopenia,
- multiple bone fractures,
- varying degrees of blue sclerae,
- teeth problems, and
- hearing loss.

There are 7 types of OI; Type I is autosomal dominant and the mildest.

Pseudoxanthoma elasticum: autosomal recessive and involves skin, blood vessels, and eyes. The main problem is recurrent UGI bleeds. Classic findings include a cobblestone appearance of the skin with yellow papules and plaques on the lateral aspect of the neck and angioid streaks on funduscopic exam. (But this also occurs in Paget disease!)

RHEUMATOID ARTHRITIS

OVERVIEW

The prevalence of RA in the U.S. is ~ 0.5–1%. Women outnumber men 3:1. The typical age of onset is 40–50 years. Etiology of RA is multifactorial and basically unknown. There is a low concordant incidence of RA in identical twins, but RA does seem to have some genetic basis (~ 10% of patients have a 1st degree relative with RA; higher concordance in identical twins than in fraternal ones).

Not all patients with RA develop destructive arthritis, but we have no definitive way of determining which patients will develop erosive disease, so rheumatologists have a low threshold for treating patients aggressively. A few lab and clinical indicators suggest aggressive disease.

As mentioned under Labs, rheumatoid factor (RF) is positive in 80–85% of patients with RA, but it is not specific. It may take up to 2 years before the RF becomes positive.

Know that anti-CCP antibody:

- appears earlier than RF,
- has greater specificity for the diagnosis of RA (97%), and
- is associated with development of erosive RA.

In the new and most current diagnostic criteria for RA, RF and anti-CCP antibodies play a prominent role in the diagnostic criteria. A high titer of either one contributes 3 of the required 6 points for the diagnosis.

A severe course of RA is probable in a patient with:

- HLA-DR4 antigen,
- high-titer RF or anti-CCP antibodies,
- multiple joint involvement,
- constitutional symptoms,
- early radiographic evidence of erosive disease, and
- extraarticular disease (e.g., rheumatoid nodules).

In an affected RA joint, there is an inflamed synovium (with increased type A and B synovial cells). In its chronic phase, this inflamed membrane of granulation tissue (pannus) stimulates the release of multiple cytokines, which leads to cartilage destruction, bone erosion, and an inflammatory synovial fluid that has decreased viscosity.

Present in the synovium of the rheumatoid joint are cytokines and chemokines, which are secreted by activated lymphocytes, macrophages, and fibroblasts; these probably account for most of the destructive effects of RA. They include:

- interleukins (especially IL-1 and IL-6; important when considering treatment for RA),
- interferons,
- colony-stimulating factors (CSF),
- growth factors, and
- tumor necrosis factor (TNF-α; also important when considering treatment for RA).

SIGNS / SYMPTOMS OF RA

Signs and symptoms of RA include 1 to several hours of morning stiffness, fatigue, low-grade fever, anorexia, and weight loss. Remember: Noninflammatory joint diseases, such as OA, cause < 30 minutes of stiffness.

QuickQuiz

- Which factors suggest aggressive RA?
- How long is the typical morning stiffness in RA? In OA?
- What are the diagnostic criteria for RA?
- What is the pattern of arthritis in RA?
- Which part of the spine is sometimes involved in RA? Which parts are never involved?

Buzzwords for both RA and SLE: The arthritis is symmetric and polyarticular. There is specific involvement of the hands—especially the MCP and PIP joints (Image 6-2); the DIP joints are spared! Boutonnière and swan-neck deformities occur in advanced disease, although they are nonspecific for RA.

Symptoms of RA may be intermittent (15–30%) or progressive. Intermittent disease has remissions lasting up to 1 year.

Know the diagnostic criteria for RA, which changed in 2010. A complete list of criteria can be found in the 2010 ACR/EULAR guidelines on the American College of Rheumatology website at www.rheumatology.org.

From this, remember the following essentials. RA can be diagnosed when all of the following are present:

- Inflammatory arthritis of ≥ 3 joints
- +RF and/or anti-CCP
- Increased ESR or CRP
- Duration > 6 weeks

Other causes must be excluded (especially if symptoms have been present for < 6 weeks), such as SLE, Sjögren's, overlap syndromes, sarcoidosis, and viral reactive arthritis.

Seronegative RA is diagnosed when patients meet other criteria but lack RF and anti-CCP. These patients tend to have less severe disease than what is seen in antibody-positive patients.

John Watney Photo Researchers, Inc

Image 6-2: Rheumatoid arthritis of the metacarpophalangeal joints, with an endarteritis-associated ulcer on dorsum

Hemochromatosis is another disease that commonly involves the 2nd and 3rd MCP and PIP joints, but the arthropathy of hemochromatosis is distinctly asymmetric. Also, hemochromatosis has hook-like osteophytes on the MCP joints and chondrocalcinosis—neither finding is seen in RA. Patients can easily be screened for hemochromatosis with iron studies. An elevated transferrin saturation (Fe/TIBC of > 45%) or elevated ferritin level suggests the diagnosis. Know these clues for differentiating RA and SLE from hemochromatosis.

Hoarseness, sore throat, and/or neck pain may indicate involvement of the cricoarytenoid joint in the patient with RA. The temporomandibular joints also may be affected.

The knee is the most common single joint initially involved in RA; but small joints—in a symmetric fashion—are more commonly involved over time. In fact, the forefoot has proven to be the site of earliest radiographic changes in RA, and the head of the 5th metatarsal bone may be the location of the earliest erosion. Carpal tunnel and tarsal tunnel syndromes can occur in RA. If a patient with inflammatory knee arthritis presents with a swollen calf, suspect a ruptured Baker cyst (popliteal cyst) causing pseudophlebitis. Occasionally, a Baker cyst can cause extrinsic venous compression that can simulate a deep vein thrombosis.

C-spine: Patients with chronic, severe disease may develop cervical instability at the atlantoaxial articulation (C1–C2).

While patients can be asymptomatic, suspect this when a patient with RA complains of:

- recurrent occipital headaches,
- limited neck range of motion, or
- paresthesias of the hands and feet.

If these symptoms are present, order cervical spine x-rays with flexion and extension views. In RA patients scheduled to undergo endotracheal intubation, an evaluation for cervical instability is mandatory. Acute subluxation, which may occur with extension of the neck for intubation, can cause spinal cord compression or vertebral artery compression leading to quadriparesis or sudden death. Remember: All patients with long-standing RA should have flexion and extension neck films before surgery to assess for subluxation.

The thoracic, lumbar, and sacral spine and, usually, the SI joints are spared in RA (in contrast to ankylosing spondylitis and psoriatic arthritis). Again, RA does not present as lumbar spine pain. If you see a patient with

RA and spine pain, think about the myriad other potential causes of spine pain; e.g., compression fractures—not a flare of RA.

EXTRAARTICULAR MANIFESTATIONS

Remember: Extraarticular manifestations of RA are very unlikely in the setting of absent RF and anti-CCP antibodies (seronegative RA). Know these extraarticular manifestations of RA:

Cardiac:

- Pericarditis (with effusion or thickening) and myocarditis
- Rheumatoid nodules on the valves
- Atherosclerosis—3x increased risk of atherosclerotic cardiovascular disease (sudden death and MI). Coronary artery disease is the leading cause of death.

Renal (all very rare):

- Drug-related renal disease
- Amyloid renal disease occurring late in rheumatoid arthritis

Lungs (males more often):

- Exudative pleural effusion with low glucose (< 30 mg/dL) and pH.
- Diffuse interstitial fibrosis and intrapulmonary rheumatoid nodules; when caused by mine dust, it is called Caplan syndrome (mine dust pneumoconiosis).

Vasculitis:

- May resemble polyarteritis nodosa and cause nailfold infarcts.
- Necrosis with ulceration may occur, especially over the malleoli.

Nerves:

- Mononeuritis multiplex, which may manifest as foot or wrist drop
- Carpal tunnel syndrome
- Cervical myelopathy

Eyes:

- Episcleritis
- Scleritis
- Sicca

Skin:

- Rheumatoid nodules occur in 25% and indicate potential for more severe disease. These nodules usually appear on extensor surfaces but may also be found in the lungs and on heart valves.

Blood and lymphatics:

- Anemia of chronic disease
- Neutropenia (seen in Felty syndrome and large granular lymphocyte [LGL] syndrome)
- Increased risk of lymphoma

Felty syndrome consists of the classic triad of rheumatoid arthritis, splenomegaly, and neutropenia. These patients usually have long-standing disease associated with high titers of rheumatoid factor and subcutaneous rheumatoid nodules and suffer increased mortality from infections. Treatment: methotrexate, cyclosporine A, corticosteroids, granulocyte colony-stimulating factor (GCSF), and, if needed, splenectomy. If splenectomy is ineffective, the prognosis is poor. TNF inhibitors are currently being evaluated.

Large granular lymphocyte (LGL) syndrome may be difficult to distinguish from Felty syndrome since it also presents with neutropenia, splenomegaly, and susceptibility to infections. It differs from Felty syndrome in that it is less associated with RA and rarely may progress to LGL leukemia. Also, in contrast to Felty syndrome, these patients do poorly with splenectomy.

TREATMENT OF RA

Overview

Drugs used to treat RA (see Table 6-5) are categorized as:

- nonbiologics (nonsteroidals and disease-modifying antirheumatic drugs [DMARDs]),
- immunosuppressants,
- biologics, and
- miscellaneous.

Trials show that 70% of patients with active, polyarticular, RF-positive disease develop joint damage or erosions within 2 years of onset. Other trials show that early treatment with a DMARD may alter the course of the disease. Trials with combination DMARDs in early disease also show benefit. NSAIDs may help with inflammation and pain, but do not prevent the formation of either erosions or joint deformities. Glucocorticoids, like DMARDs, can alter the course of disease but are associated with significant long-term side effects.

Previously, treatment of RA followed a pyramid regimen consisting initially of NSAIDs and glucocorticoids—with DMARDs added only as the disease got progressively worse. Now we know that RA-associated disability can be drastically reduced when we treat early disease aggressively. Because DMARDs carry significant side effects and potential complications, today's goals focus on treating early and aggressively those patients predicted to have erosive disease (sparing patients with milder disease).

Quick Quiz

- What is the most common manifestation of RA in the lungs?
- What is Felty syndrome?
- Name some indicators of active RA. If a patient has these indicators, when do you start treatment? With what?

To review, it's tricky to tell which patients will end up with erosions, but we have some lab and clinical indicators of active disease. Know: RA patients with the following should receive early treatment (within 3 months of symptoms) with a DMARD such as methotrexate:

- Constitutional symptoms
- Progressive synovitis
- Rheumatoid nodules
- Vasculitis
- Extraarticular manifestations
- High ESR and/or CRP
- High-titer rheumatoid factor or anti-CCP
- Erosions on plain radiographs
- HLA-DR4 (not usually necessary to evaluate)

Remember that the anti-CCP antibody increases the risk of erosive disease. Rheumatologists are not definitive about how to incorporate anti-CCP in planning treatment if the patient does not have synovitis. When both RF and CCP antibodies are absent, there is less risk of erosive disease.

Table 6-5: Drugs Used to Treat RA

Nonsteroidals	Nonselective (e.g., ibuprofen, naprosyn, non-acetylated salicylates) and COX-2 inhibitor
Nonbiologic DMARDs	Methotrexate, leflunmide, hydroxychloroquine, sulfasalasine, gold
Immunosuppressants	Azathioprine, chlorambucil, corticosteroids, cyclophosphamide, cyclosporine, mycophenolate mofetil, tacrolimus
Biologics	TNF inhibitors (monoclonal antibodies and soluble receptors), IL-1 and IL-6 antagonists, anti-B cell antibody, T-cell inhibitor
Miscellaneous	Acetaminophen, colchicine, dapsone, IVIG, plasmapheresis/plasma exchange, thalidomide, intraarticular viscosupplementation

Biologics are added early in patients whose disease does not completely respond to DMARDs +/– corticosteroids and NSAIDs. Recognize that glucocorticoid use in RA is controversial—influenced by the efficacy of the biologics and the well-known side effects of systemic glucocorticoids. Generally, as the patient improves on early aggressive therapy, the more toxic drugs are withdrawn, while therapy continues with the less toxic ones.

Now we'll discuss these RA medications in more detail.

NSAIDs

NSAIDs are part of the initial treatment. NSAIDs decrease inflammation and joint swelling but do not alter the course of the disease. Again, know that in patients with predictors of aggressive disease, treat initially with a DMARD. NSAIDs are added to help control pain.

For patients with ASA allergy, use a sodium, magnesium, or choline salicylate. These nonacetylated salicylates do not cause an ASA allergy reaction and also may have less GI toxicity (but may be less effective).

What about the COX-2 inhibitors? Selective COX-2 inhibitors, like other NSAIDs, inhibit cyclooxygenase-2 but, unlike other NSAIDs, do not inhibit cyclooxygenase-1. Currently, the only COX-2 inhibitor available in the U.S. is celecoxib (Celebrex®), which is approved for treatment of RA, OA, ankylosing spondylitis, and acute pain (and adjunctive for familial adenomatous polyposis).

In theory, the antiinflammatory effects of COX-2 inhibitors are comparable to other NSAIDs, with reduced GI irritation and ulcer development.

Other benefits of selective COX-2 inhibitors: no effect on platelet function, so bleeding time is unchanged; less risk of bleeding in anticoagulated patients; less likely than other NSAIDs to precipitate bronchoconstriction in patients with aspirin-induced asthma.

Problems with selective COX-2 inhibitors: COX-2 inhibitors increase the risk for adverse cardiac events such as myocardial infarction, stroke, heart failure, and sudden cardiac death in some patient groups. Celecoxib is contraindicated for use in patients who are in the postoperative recovery phase after artery bypass graft. One trial of 4,000 patients showed celecoxib increased risk of death or recurrent MI (~ 2x) if taken longer than 1 month after an MI. Analysis of two recent long-term adenoma prevention trials studying celecoxib concluded there is an increased risk of serious cardiovascular events that may be dose-dependent.

Patients who are allergic to sulfa appear to have a high risk of rash with these COX-2 drugs.

Know these important drug interactions: NSAIDs and lithium have common excretory pathways, so check lithium levels periodically if a patient is receiving both meds. ASA decreases the breakdown of oral hypoglycemics, so decrease dosage of these when given with ASA. All NSAIDs, selective and nonselective, may precipitate or worsen heart failure and may raise blood pressure.

DMARDs

General Characteristics

Disease-modifying antirheumatic drugs (DMARDs):

- Methotrexate (MTX)
- Leflunomide (LEF)
- Hydroxychloroquine (HCQ)
- Sulfasalazine (SSZ)

For patients who have predictors of aggressive disease or are not adequately controlled with NSAIDs, DMARDs are a major component of RA treatment. They have a slow onset of action (several months), so concurrent NSAIDs or low-dose glucocorticoids are required initially. Because of lower cost and a better side-effect profile, HCQ and SSZ are sometimes used first in cases of mild RA. Aggressive treatment with MTX is definitely recommended for patients with moderate-to-severe disease.

Methotrexate (MTX)

MTX is an antifolate agent with antiinflammatory properties that is very effective in the treatment of RA. Because it has the most predictable benefit and is usually the best tolerated, the 2008 American College of Rheumatology practice guidelines recommend MTX as the initial DMARD for patients with moderate-to-severe RA who can tolerate it (regardless of prognosis). Some patients begin to improve within 6 weeks. It is administered orally, subcutaneously, or intramuscularly once a week and is often combined with other agents to maximize disease control. Preexisting renal or liver disease (e.g., HBV, HCV, alcohol abuse) and pregnancy are definite contraindications.

Common side effects and complications of MTX include:

- Alopecia
- GI (nausea, vomiting, diarrhea, mucositis)
- Marrow suppression even at low doses (Prescribe folate replacement 1 mg/day for prevention. Coadministration of sulfa drugs or antifolate agents can worsen cytopenias, so follow CBC.)
- Increased liver transaminases (AST/ALT)

Other serious, but less common, reactions to be aware of include:

- increased susceptibility to opportunistic infections,
- severe hepatotoxicity (follow AST/ALT),
- nephrotoxicity (follow creatinine), and
- pneumonitis/pulmonary fibrosis.

The MTX pneumonitis is idiosyncratic (i.e., non–dose-related). Initial symptom is nonproductive cough. Radiograph is initially normal but shows alveolar infiltrates in later stages.

MTX-related toxicities are not age-related. Monitor transaminases, creatinine, and CBC every 4–8 weeks. A baseline CXR is recommended. Order pulmonary function tests in patients with symptoms of dyspnea or a history of COPD (pay attention to the DLCO). Monitoring renal function is important because most of MTX is excreted unchanged in the urine. Renal failure from any cause will lead to accumulation of this drug and increased toxicity. Live virus vaccines are contraindicated (MMR, varicella, oral polio, yellow fever).

Leflunomide (LEF)

LEF (Arava®) is used only to treat RA. It is a pyrimidine antagonist and recommended by 2008 RA practice guidelines as the initial DMARD in patients unable to take MTX.

Its side effects are very similar to MTX. Minor adverse reactions include diarrhea and respiratory infections. Its major side effect is hepatotoxicity, and it should be avoided in those with preexisting liver disease. Other important side effects include cytopenias, renal dysfunction, interstitial lung disease, and opportunistic infections.

Screen for latent TB before prescribing this drug. CBC and LFTs need to be monitored frequently, as with MTX. The drug is contraindicated in pregnancy and unsafe for lactation. Also, do not vaccinate with live viruses.

Important: Because LEF has an extremely long half-life and is teratogenic, women planning to conceive must discontinue the drug and undergo treatment with cholestyramine to eliminate the drug.

Hydroxychloroquine (HCQ)

Patients on HCQ need biannual ophthalmologic evaluation for possible retinopathy. Check renal function at least once a year. If renal dysfunction occurs, the risk of ophthalmic toxicity rises greatly (usual risk considered to be 1/5,000 patients after prolonged usage). Check CBC annually with prolonged therapy. Also monitor muscle strength periodically because of the risk of myopathy. Know that use of HCQ in psoriatic patients may exacerbate their rash.

Quick Quiz

- Which DMARDs are used to treat mild RA?
- Which DMARD is recommended by the American College of Rheumatology as 1st line for all moderate-to-severe cases of RA?
- What are methotrexate contraindications?
- Name another DMARD recommended to treat RA in patients who cannot tolerate methotrexate.
- What follow-up is required in patients treated with hydroxychloroquine?
- What are the categories of biologics used to treat RA? What are representative drugs for each?
- Name some serious complications of the various biologics.
- What is the most common side effect of the biologics?

Sulfasalazine (SSZ)

Also used for inflammatory bowel disease (IBD). In RA, the sulfapyridine portion of the molecule produces effects; in IBD, the 5-amino salicylic acid (5-ASA) portion is the effective component. The most common side effects are sulfa-allergic reactions, nausea, vomiting, diarrhea, and crampy abdominal pain. It may cause reversible oligospermia (no effect on female reproduction), cytopenias, and an elevation in transaminases (monitor with periodic CBC and LFTs). The 5-ASA component can cause Reye syndrome in patients vaccinated with the varicella vaccine (because it's a live virus vaccine).

Minocycline or Doxycycline

These drugs are not FDA-approved for RA. They are occasionally beneficial as mild DMARDs for some RA patients because of their metalloproteinase inhibition, although they may be more effective for the spondyloarthropathies.

Biologic Agents

See Table 6-6 on page 6-12 for a synopsis of the biologics currently approved for RA. Infliximab, adalimumab, certolizumab, and golimumab are antibodies that bind and inactivate tumor necrosis factor (TNF), an important mediator of the inflammatory response in RA. Etanercept is a soluble TNF receptor that is linked to IgG1 and also binds and inactivates TNF. The anti-TNF drugs are approved for a variety of uses, including RA, psoriasis, ankylosing spondylitis, and inflammatory bowel disease. Know: For RA, these agents are most beneficial when combined with methotrexate and have been shown to halt and possibly heal erosive changes!

Interleukin antagonists (anakinra = IL-1; tocilizumab = IL-6) are used to treat RA refractory to the MTX/TNF inhibitor combination.

Rituximab is an anti-CD20 antibody directed against B cells, which are believed to mediate progression of RA. It is used in combination with MTX to treat RA in patients refractory to TNF inhibitors.

Abatacept is a T-cell inhibitor used to treat refractory RA. Activated T cells are increased in the synovium of people with this disease.

Most of these agents have received FDA boxed warnings for an increased risk of serious infections (e.g., disseminated fungus and tuberculosis—both primary and reactivation). Infliximab has also received a warning for increased risk of heme malignancies. Rituximab has a slightly different set of warnings: an increase in mucocutaneous complications (Stephens-Johnson syndrome, toxic epidermal necrolysis), progressive multifocal leukoencephalopathy, tumor lysis syndrome, and deadly infusion reactions (hypotension, bronchospasm, acute respiratory distress syndrome, MI).

Know that you should avoid live virus vaccines in patients prescribed a biologic, and all patients should be screened annually for tuberculosis. These potential complications sound terrible (and they are!), but know that they are not common—the most common side effect is an increase in upper respiratory tract infections.

Patients with active infections need to discontinue or delay treatment until the infection has resolved. Less common, but noteworthy, complications include worsening psoriasis and reactivation of HBV.

The TNF inhibitors may cause CNS demyelination, precipitation or exacerbation of heart failure, and a SLE syndrome with positive ANA and anti-dsDNA antibodies.

Immunosuppressants

Glucocorticoids

Low-dose oral prednisone (< 10 mg/d or equivalent) and joint injections of glucocorticoids are very effective for relieving the symptoms of RA. Joint injections have dramatic but temporary effects on symptoms but do not slow the systemic disease process. Low-dose oral glucocorticoids may decrease the rate of erosion; however, the negative side effects of glucocorticoids limit their use—although the bisphosphonates appear to protect against osteopenia in this group. Even low-dose glucocorticoids must be tapered slowly in RA patients.

Azathioprine (AZA)

AZA has shown some benefit, but is much more commonly used in SLE. Its main side effects include bone marrow suppression, N/V, diarrhea, and hepatotoxicity.

It is important to know about AZA's metabolism. It is first metabolized to 6-mercaptopurine (6-MP) by the liver. AZA and 6-MP are inactive prodrugs. 6-MP can then be metabolized by 3 different pathways. Two are important to know:

1) Thiopurine methyltransferase (TPMT) is an enzyme in the main metabolic pathway for 6-MP. Patients with heterozygous or homozygous mutations in this enzyme (10% of population) are prone to severe AZA toxicity. Some experts recommend testing for this mutation because patients with this deficiency should be given lower doses of AZA.
2) Xanthine oxidase (XO) is an enzyme in another important metabolic pathway for 6-MP. This is important because allopurinol, a drug that inhibits XO, can lead to increased toxicity. The recommendation is to decrease the dose of AZA by 1/2 to 3/4 in the patient on allopurinol and to monitor CBC and LFTs closely.

Cyclosporine A

In doses of 2.5–4 mg/kg/day, it has been shown to have synergistic effects when added to MTX, but its use has been limited by renal toxicity.

Cyclophosphamide

In RA treatment, use is limited to treating RA-associated vasculitis.

SERONEGATIVE SPONDYLOARTHRITIS

Seronegative spondyloarthritides are a group of inflammatory arthritides which are called "seronegative" because the rheumatoid factor and ANA are typically negative. These arthritides have been categorized as "axial" or "peripheral," depending on which

Table 6-6: Biologics

Drug Name	Brand Name	Approved Use	Most Common Side Effects
TNF-α Inhibitors: Monoclonal Antibodies			(Boxed Warnings: Serious infections and TB)
Infliximab	Remicade®	RA, P, AS, Crohn's, UC	URI
Adalimumab	Humira®	RA, P, AS, Crohn's	URI
Certolizumab	Cimzia®	RA, Crohn's	URI
Golimumab	Simponi™	RA, P, AS	URI
TNF-α Inhibitors: Soluble Receptor			(Boxed Warnings: Serious infections and TB)
Etanercept	Enbrel®	RA, P, AS	URI
IL-1 Antagonist			(Boxed Warnings: Serious infections)
Anakinra	Kineret®	Refractory RA	Neutropenia
IL-6 Antagonist			(Boxed Warnings: Serious infections and TB)
Tocilizumab	Actemra®	Refractory RA	URI
Anti-CD20			(Boxed Warnings: See text)
Rituximab	Rituxan®	RA (with MTX) anti-CD20+ NHL anti-CD20+ CLL	Fever Nausea Cytopenias
T-cell Inhibitor			
Abatacept	Orencia®	Refractory RA	Infections

RA = rheumatoid arthritis; P = psoriasis; AS = ankylosing spondylitis; UC = ulcerative colitis; NHL = non-Hodgkin lymphoma; CLL = chronic lymphocytic leukemia; MTX = methotrexate

Quick Quiz

- What are common features of spondyloarthropathies?
- "Bamboo spine" is a buzzword associated with which disease?
- How does a patient with ankylosing spondylitis present?

manifestation is primary in the presentation. These include:

- Ankylosing spondylitis (most common of the group)
- Reactive arthritis
- Psoriatic arthritis
- Axial arthropathy associated with inflammatory bowel disease (IBD)

Seronegative spondyloarthritides share some common features:

- Predilection for the spine, SI joints, and entheses (where the tendons, ligaments, and joint capsules attach)
- Asymmetric, large-joint oligoarthritis, usually of the lower extremities
- Variable association with HLA-B27

Enthesitis refers to inflammation at the insertion site of a ligament, tendon, or joint capsule. Enthesitis on the finger leads to the appearance of the "sausage digit."

Again, sacroiliitis and thoraco-lumbar and sacral spine inflammation do not occur in RA! Sausage-shaped digits are common in the spondyloarthropathies but not in RA. When the "sausage digit" buzzword is combined with "pitted nails," the diagnosis is psoriasis!

ANKYLOSING SPONDYLITIS

Overview

Ankylosing spondylitis (AS) is a systemic disease marked by axial inflammation, which, if left untreated, leads to eventual spinal and SI joint fusion resulting in a radiographic "bamboo spine" (Image 6-3). Adults, more so than juveniles, have more upper body involvement. Patients have significant morning stiffness/pain, which is improved with activity. Most adults with ankylosing spondylitis have symptomatic painful sacroiliitis, although for some individuals, mild stiffness is the only complaint.

Usual onset is in young adulthood and affects men more than women (2–3:1). Teens eventually diagnosed with AS may present with lower extremity large-joint oligoarthritis and have a 90% incidence of HLA-B27–positive antibodies.

There is only a 60% occurrence of ankylosing spondylitis in identical twins, so environmental factors also play a role.

Extraarticular manifestations of AS include:

- uveitis,
- ischemic heart disease,
- aortic insufficiency,
- apical pulmonary fibrosis, and
- IgA nephropathy.

Eye disease may precede sacroiliitis and usually presents as unilateral pain, photophobia, and increased lacrimation. Apical pulmonary fibrosis is a late and rare manifestation that can be associated with pulmonary restriction. IgA nephropathy is associated with AS and should be suspected in any patient with AS who develops an active urine sediment. These patients should be sent immediately to a nephrologist for renal biopsy.

Diagnosis

Suspect AS when a patient is < 45 years of age and has symptomatic inflammatory back pain for > 3 months in the absence of inflammatory bowel disease or psoriasis. Limited mobility in the spine and in expansion of the chest, flexion deformities of the hip, peripheral joint arthralgias, enthesitis, and dactylitis are additional supportive symptoms.

Inflammatory back pain has different characteristics compared to other causes of back pain (e.g., disc disease). Classic "inflammatory" back pain occurs for longer than 3 months in a young patient < 40 years of age, is gradual in onset, improves with exercise and not with rest, and worsens when sleeping and lying flat.

Radiographic signs of sacroiliitis (calcification and SI joint fusion resulting in the "bamboo spine" deformity) may be absent for > 10 years after onset of symptoms. MRI is more sensitive and shows "marrow edema" in the bones adjacent to the SI joints. Regardless, radiographic changes often are not seen at the time of diagnosis. The clinical and laboratory evaluation is most important in patients with early symptoms.

HLA-B27 test is generally done. Because of the high sensitivity (> 90%), a negative HLA-B27 test is useful in excluding AS in patients. Because of its low specificity, it has little use in supporting the diagnosis of AS.

Image 6-3: Bamboo spine; Ankylosing spondylitis

A condition that can be confused with AS because it can present similarly is diffuse idiopathic skeletal hyperostosis (DISH). In contrast to AS, DISH primarily occurs in men > 50 years of age, does not affect the SI joint, and is not associated with HLA-B27. Classic x-ray findings in DISH include "flowing" osteophytes anterior to the spinal ligaments. The word "flowing" is used because these calcifications have the appearance of someone pouring candle wax in front of the vertebrae. Inflammatory markers (ESR/CRP) are typically normal in DISH, but may be elevated in AS.

Treatment

As we learn more about AS, treatment goals are changing. Traditionally, spinal and SI joint fusion was non-preventable, so the goal was to help the patients fuse their spines in a functional position. To some degree, this is still the goal, so main forms of treatment include stretching exercises, posture training, and proper pillow positioning during sleep (sometimes no pillow is best).

As our understanding of spondyloarthritides evolves, treatment is changing. Controversy remains among rheumatologists about how best to treat AS. Bottom line:

- All patients should be on an exercise program.
- NSAIDs are good analgesics.
- Systemic steroids are not recommended.
- Patients with primarily peripheral disease can be treated with sulfasalazine or methotrexate.
- Axial disease usually is treated with a biologic drug. Know that the DMARDs sulfasalazine, methotrexate, and leflunomide are not useful for axial disease.

If the diagnosis is made early, the prognosis is generally good, but more than 20% of patients have progressive, disabling disease.

REACTIVE ARTHRITIS

Overview

The most common cause of acute, nontraumatic arthritis in a person under the age of 50 is reactive arthritis, which is an immunologic reaction to an infection elsewhere in the body—typically genitourinary (GU) or gastrointestinal (GI) infections. Common causes of reactive arthritis are a GU infection from *Chlamydia trachomatis* and GI infections due to *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, and *Clostridium difficile*. It is also seen in those with common viral illnesses (e.g., enterovirus) and HIV infection. The arthritis typically develops within 2 months of the infection, but the responsible organism usually is not identified. While reactive arthritis is the most common cause of an acute nontraumatic arthritis, it is a very uncommon cause of a spondyloarthritis—AS is more common.

Reactive arthritis most commonly presents as an asymmetric, mono- or oligoarticular arthritis of the lower extremities. Enthesitis is common and characteristic, especially at the insertion points of the Achilles tendon and the plantar fascia. Axial spine pain is not a common feature but it can occur, thus, the categorization of reactive arthritis as a spondyloarthritis.

Other reactive arthritis associations include keratoderma blennorrhagicum and mucocutaneous genital lesions and/or mouth ulcers. Keratoderma blennorrhagicum resembles the lesions of pustular psoriasis. Circinate balanitis is a type of mucosal genital lesion seen in males. The classic triad of urethritis, conjunctivitis, and asymmetric arthritis is seen in fewer than 1/3 of patients.

Diagnosis can be tough because the inciting infection often is resolved when the arthritis presents. This is especially true of the enteric pathogens. DNA amplification for genital *Chlamydia* is recommended in patients who have no obvious cause in their history, because *Chlamydia* infections can be asymptomatic, even in males. If a peripheral joint is swollen, arthrocentesis is recommended to exclude bacterial infection and crystalline arthropathies. HLA-B27 testing is not helpful in this entity. Radiographs are helpful if osteoarthritis is a possible alternative diagnosis.

Treatment

NSAIDs are recommended for initial treatment. Systemic steroids are used short-term in patients who have refractory arthritis. For severe or disabling disease, sulfasalazine or methotrexate is used. TNF inhibitors are used rarely and only in extreme refractory cases (Table 6-6 on page 6-12).

Antibiotics typically are not helpful once the reactive arthritis occurs but are important in the acute infection to prevent the reactive arthritis component. Recurrent symptoms do not require repeat antibiotic regimens if the initial infection was treated properly.

Reactive arthritis should be at the top of your list for any patient < 50 years old who develops an acute, asymmetric large-joint arthritis in the setting of a recent gastrointestinal or genitourinary infection. Quiz patients about any recent illnesses, especially diarrhea or urethritis/STD (usually during the prior 2–4 weeks) but also ask about viral infections and conjunctivitis.

ENTEROPATHIC ARTHROPATHY

Enteropathic arthropathy presents primarily as an asymmetric peripheral oligoarthritis of the lower extremities that occurs with flare-ups of inflammatory bowel disease, followed by complete remission of the peripheral synovitis as the bowel disease improves. The peripheral arthritis involves only a few joints in the lower extremities. Patients may also present with symmetric polyarticular arthritis of the hands, as seen in RA.

QuickQuiz

- Which organisms are associated with reactive arthritis?
- What is the classic triad of findings seen in reactive arthritis?
- What are the patterns of arthritis seen with psoriasis? Name some other associated features.
- Which drug, sometimes used in treatment of arthritis, might exacerbate the psoriatic rash?
- "Sausage-shaped digits" are seen in which arthritides?

Extraarticular manifestations such as erythema nodosum, pyoderma gangrenosum, and inflammatory eye disease also parallel the flare-ups of IBD.

About 20% of patients have spine and sacroiliac involvement that mimics AS and runs a course independent of the bowel disease (or sclerosing cholangitis, which is associated with IBD). These symptoms do not worsen or improve in response to IBD flares or improvements.

Therapy for the bowel disease (i.e., sulfasalazine, corticosteroids, azathioprine), may control the peripheral joint symptoms and extraarticular manifestations. Anti-TNF agents may be required to control the spine arthropathy.

PSORIATIC ARTHRITIS

Arthritis with psoriasis is more often seen in patients who have more than just the rash. 20–30% of patients who have nail pitting, onycholysis (separation of the nail from the nail bed), and "oil spots" (brownish discoloration under the nails) develop joint disease, whereas only 7% of patients who simply have rash develop arthritis (Image 6-4).

Joint involvement in psoriatic arthritis can have varying presentations. It can present very similarly to RA (symmetric polyarthritis) or as asymmetric joint involvement, enthesitis, spondylitis, and dactylitis (sausage-like digits). Sacroiliitis is usually asymmetric and is seen in 20%. Hand DIP joints are commonly involved in patients with psoriatic nail disease. (To review, remember that the RA synovitis involves MCPs and PIPs, but not DIPs!) (Figure 6-1 on next page.) In the worst-case arthritis scenario, patients have a severe, resorptive degeneration of the joints called "arthritis mutilans."

Treatment: starts with NSAIDs, which can control pain and inflammation, but NSAIDs do not alter the natural course of disease or prevent joint destruction. Treatment is very similar to RA, with MTX being the predominant DMARD used in patients with disease refractory to NSAIDs. Anti-TNF agents are used primarily in those patients with plaque psoriasis and with erosive disease that fails to improve with a nonbiologic DMARD. In something of a paradox, however, we are now seeing an increase in psoriasis in RA patients who are treated with anti-TNF drugs. Discontinuing the drug makes the new rash go away. Cyclosporine A is effective and may be combined with MTX to control both the joint and skin disease (monitor renal function).

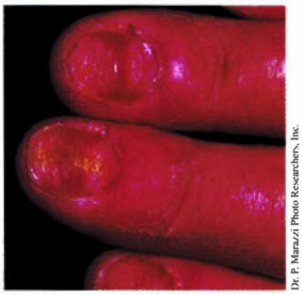


Image 6-4: Dystrophic, pitted nails in a patient with psoriasis

Avoid antimalarial drugs (e.g., hydroxychloroquine), lithium, and beta-blockers in psoriatic arthritis because they often exacerbate the skin disease. Systemic corticosteroids should also be avoided because their withdrawal can lead to a severe, life-threatening form of pustular psoriasis. Other conditions that exacerbate psoriasis include sunburn, viral infections, and strep pharyngitis.

AGAIN

Just to review: Sausage-shaped digits are common only in reactive arthritis and psoriatic arthritis. Ice pick-like pitting of the nails is very specific for psoriatic arthritis. Causes of DIP and PIP synovitis are limited (reactive and psoriatic only).

OSTEOARTHRITIS

Osteoarthritis (OA) can be primary (idiopathic) or associated with inflammatory arthritis, such as gout and pseudogout. It's unclear whether the OA or the crystalline arthropathy comes first, although most experts think the latter. OA also can arise after joint damage due to hemochromatosis, neuropathic joints due to diabetes, and trauma. OA pain characteristically worsens with excessive activity and progresses slowly with an insidious onset (contrary to the inflammatory arthritides, such as gout and RA).

The pattern of OA synovitis is classically nonerosive, asymmetric, and without calcium deposition in the cartilage (termed "chondrocalcinosis"). Most commonly affected joints are hands, feet, knees, hips, and the spine. Synovitis of the ankle, wrist, and elbow is very rarely due to OA. If a patient's symptoms include swelling of one of these 3 joints, chondrocalcinosis, or any obviously symmetric, erosive synovitis, think about other causes—not OA!

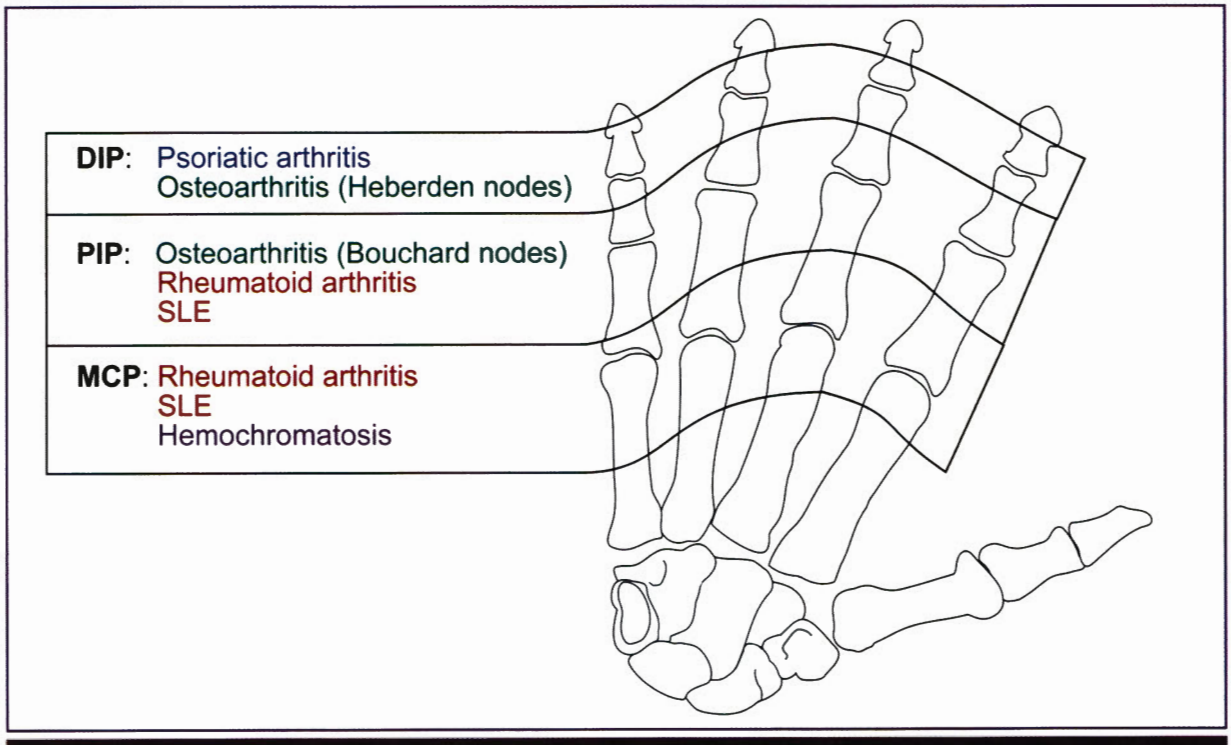


Figure 6-1: Hand Joints Affected by Rheumatologic Diseases

OA of the hands: Changes most often affect PIPs and DIPs and may be associated with classic enlargements called Bouchard (PIP) and Heberden (DIP) nodes. There is controversy about whether the nodes result from osteophyte formation or development of small cysts around the joints. Occasionally, these nodes can become inflamed and very tender. The enlargement of the hand joints is asymmetric, hard, and bony—not soft and spongy, as with inflammatory arthritis; OA rarely affects MCPs (metacarpophalangeal joints).

Diagnosis of hand OA is supported when there is pain in the hands and 3 of the following clinical criteria (sensitivity 94%; specificity 87%):

- Bony enlargement of 2 or more: DIPs/PIPs of 2nd and 3rd fingers and 1+ carpometacarpal joints
- Bony enlargement of > 2 DIPs
- Fewer than 3 MCP swellings
- Deformity of 1 of the 10 DIPs/PIPs

Labs and radiographs do not increase the diagnostic yield.

Hip OA: Pain is usually exertional and in the groin area (as opposed to the lateral thigh, which is more often seen with trochanteric bursitis), but it can also be experienced as radiation to the knee.

Diagnosis is supported by hip pain and 2 of the criteria below (and exclusion of other diagnoses):

- ESR < 20 mm/hr
- Femoral or acetabular osteophytes on radiograph
- Joint space narrowing on radiograph

Radiographs and labs do increase diagnostic sensitivity and specificity (89% and 91% respectively, if these criteria are used).

Knee OA: Pain is usually exertional and characterized as a deep ache superior to the patella or deep inside the knee joint. Pain described as medial and inferior to the joint is more likely to be from pes anserine bursitis. And don't forget that pain from hip OA can radiate to the knee. (See Image 6-5.)

Suspect knee OA when the case includes pain and several of the following features:

- Age usually ≥ 50 years
- Morning stiffness < 30 minutes
- Bony enlargements (especially if age is < 40 years)
- Crepitus
- Noninflammatory synovial fluid (200–2,000 WBCs/mm^3)
- ESR < 20 mm/hr
- Osteophytes on radiograph

The more data you have in combination, the more confident you can be about an OA diagnosis. Clinical criteria alone are about 90% sensitive and specific (higher with labs and radiographs).

QuickQuiz

- Which joints of the hand are affected in osteoarthritis?
- What characteristic features are seen in the hands of patients with OA?
- What diagnoses do you consider when you see the pattern of DIP and PIP swelling?
- What is the pattern of synovitis in osteoarthritis?
- Characterize the joint fluid from synovitis due to OA.

Treat OA with education (weight loss, exercise, and shoe insoles) and analgesics for pain relief (acetaminophen at maximum dose of 3 g/day and/or NSAIDs). Tramadol alone, or in combination with acetaminophen ± NSAID or celecoxib, is helpful for refractory pain. Long-term opiates should be avoided, especially in the elderly.

Intraarticular glucocorticoids are useful in patients unable to tolerate NSAIDs, receive inadequate analgesia from acetaminophen, and/or have only 1 or 2 painful joints. Limit intraarticular steroid injections to no more than 3–4 a year.

Intraarticular injection of hyaluronic acid is also effective in reducing pain in some patients, compared to placebo; it is equivalent to long-term analgesics. Some patients who do not respond to intraarticular steroids respond to hyaluronic acid. Watch out for post-injection flare of joint inflammation.

Randomized, placebo-controlled trials and meta-analyses have shown no difference in pain with glucosamine + chondroitin, but the combination is not harmful. Glucosamine should not be used if the patient has an allergy to shellfish.

If the patient does not respond to the above therapies, knee replacement is indicated.

Image 6-5: Standing radiographs of the knees showing severe OA with loss of joint spaces

CRYSTAL ARTHRITIS

GOUT

Uric acid gout is caused by an excess of uric acid in the serum with deposition into joints causing recurrent bouts of acute arthritis and, ultimately, chronic arthropathy. Crystals also can accumulate in tissues causing tophi and kidney stones.

Acute gout usually presents after years of sustained hyperuricemia—in male patients > 40 years of age, and after menopause in females (estrogen appears to be a uricosuric agent). Comorbidities and drugs can modify when disease presents, however.

The following are predisposing factors for development of acute gouty arthritis:

- Intake of beer or liquor (not wine) in males
- High intake of fatty foods, meat, and seafood (higher the intake, more likely to develop gout)
- Trauma
- Surgery
- Starvation
- Drugs: thiazide and loop diuretics, nicotinic acid

The excess uric acid (UA) is caused by either its increased production or decreased renal excretion, although most patients with hyperuricemia never will develop gout, tophi, or nephrolithiasis.

Hyperuricemia can be primary, in which case it is usually permanent, or it can be secondary, as a result of comorbid diseases or drugs.

Decreased renal excretion of uric acid can be:

- idiopathic,

or secondary to:

- chronic renal disease,
- lead nephropathy,
- alcohol,
- drugs, or
- diabetic ketoacidosis.

Most cases of gout are due to decreased excretion.

Increased production of uric acid can be:

- idiopathic,

or secondary to:

- leukemia,
- hemolytic anemia,

- psoriasis,
- exercise,
- fructose ingestion, or
- G6PD deficiency.

To determine whether a patient is an "overproducer" or an "underexcreter," measure the amount of UA in the urine over 24 hours. Underexcreters have normal 24-hour urine UA levels in the setting of increased serum levels (or < 600 mg); overproducers often have > 800 mg per 24 hours.

Definitely do these measurements in premenopausal females and in males < 25 years of age who develop acute gout. (Often the hyperuricemia is hereditary, and many will get kidney stones.) Also, you should do these measurements if you intend to prescribe a uricosuric agent, to ensure that the patient's rate of excretion won't result in a stone if you increase the excretion rate with your drug intervention. In most other cases, these measurements usually are not performed because rarely do the results change management.

Acute gouty arthritis classically presents as an acutely tender and swollen joint that may occur at night and awakens the patient from sleep. Pain reaches maximum intensity within the first 24 hours and self-resolves within a few days to several weeks. In 50%, the initial attack occurs in the metatarsophalangeal (MTP) joint of the great toe (termed "podagra"). The knee is the next most common joint to be affected. In between attacks of acute gout, the patient is completely asymptomatic—a useful clue to help distinguish gout, if the diagnosis is in question.

Acute polyarticular gout is much less common. It is more often seen in patients with myelo- or lymphoproliferative disorders (e.g., leukemias) and post-organ transplant.

Diagnose gout by performing an arthrocentesis and looking for intracellular crystals in the joint fluid. Arthrocentesis classically shows inflammatory joint fluid with > 2,000 WBCs/mm^3 and a predominance of neutrophils. Uric acid crystals are "needle-like" and are strongly negatively birefringent under polarized light. (The crystals that are parallel to the color compensator are yellow.) To be diagnostic, the crystals must be intracellular. See Image 6-6. It is very important that the crystals be seen inside cells before gout is considered as the cause of an acute arthritis. Occasionally, urate crystals are found floating in the joints of patients who do not have gout. So, merely finding a floating uric acid crystal does not make gout the diagnosis, but finding an intracellular crystal does.

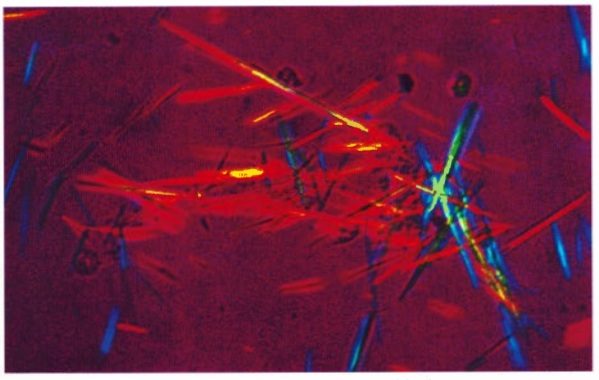

Bob J. Galindo

Image 6-6: Uric acid crystals under polarized light

Rarely, uric acid crystals will not be identifiable in the joint fluid, and the fluid characteristics may make this presentation hard to differentiate from septic arthritis. In that situation, gout is the most likely diagnosis if the patient has evidence of uric acid deposition in the tissues (e.g., linear densities overlying cartilage visible on ultrasound; uric acid deposits visible on CT; and subcortical bone cysts visible on plain radiographs or MRI indicative of bony tophi).

The uric acid level does not correlate with an attack of acute gout—often patients have normal or low levels when the acute arthritis is present. Conversely, an elevated serum uric acid does not confirm the diagnosis of gout, but it does indicate patients who are at risk. As serum UA levels increase > 9–10 mg/dL, incidence of gouty attacks increases to 5% per year.

Quick review: Gout = intracellular uric acid crystals, needle-shaped, yellow when parallel, negative birefringence.

Acute Treatment

Treat the acute attack with ice packs and intraarticular corticosteroids if only 1 or 2 joints are involved, or use NSAIDs if multiple joints are involved.

Intraarticular steroid injections are especially useful for patients with chronic kidney disease or heart failure who cannot take NSAIDs. Before using an intraarticular steroid, however, make sure that joint infection has been excluded.

Low-dose oral colchicine (1.2 mg x 1 dose, then 0.6 mg one hour later) can be used in patients who do not respond to NSAIDs or who have taken the drug in the past and had a good response. This low-dose regimen has equivalent efficacy and better tolerability when compared with the older, higher-dose regimen that caused severe vomiting and diarrhea. Avoid colchicine in patients with advanced chronic kidney disease. IV colchicine is no longer on the U.S. market because of the side effect profile.

Oral prednisone is the last option for patients who have polyarticular gout and cannot take NSAIDs or colchicine.

Antihyperuricemic drugs that are given for chronic treatment (e.g., allopurinol, febuxostat) should not be started during an acute attack of gout but can be continued if the patient is already taking one.

Quick Quiz

- How is gout definitively diagnosed?
- Characterize the crystals of gout when observed in a polarizing microscope.
- How could you treat a gout flare in a single joint?
- What drugs used for chronic treatment of gout are contraindicated during an acute gouty attack?
- With which drugs do you have to adjust downward the dose of allopurinol?

Chronic Treatment

Chronic treatment of gout includes:

- Avoidance of precipitants, including the foods and drugs mentioned above.
- A drug to reduce hyperuricemia: either a uricosuric (probenecid), which increases renal UA excretion, or a xanthine oxidase inhibitor (XOIs) (allopurinol, febuxostat), which decreases UA production. Underexcretion of UA is the most common reason for hyperuricemia, but uricosurics usually are not prescribed because adherence is quite low. Probenecid requires multiple daily doses and ingestion of > 1 gallon of water/day (to prevent stones). The drug is also ineffective in patients with low glomerular filtration. XOIs reduce the uric acid in both underexcreters and overproducers, so they are more commonly used.
- A drug to prevent the acute gout that can flare when the patient starts the antihyperuricemic drug.
- Surgical management of tophi, if necessary.

Definitely give an antihyperuricemic drug to patients with the following:

- Tophi
- Uric acid kidney stones or 24-hour urine uric acid level > 1,100 mg/day (But do not use a uricosuric drug.)
- Radiographic signs of chronic gouty arthropathy
- Recurrent acute attacks

Start chronic treatment after the acute attack resolves completely, and aim for reducing the serum UA to < 6 mg/dL. When UA levels are below 6, urate crystals are reabsorbed from the joint and tophi, resulting in improved symptoms. Usually, the drug has to be given for life; when the drug is stopped, uric acid deposition usually recurs.

Remember: Do not start a XOI during an acute attack because doing so can exacerbate the arthritis. Also, starting or re-starting the drug in an asymptomatic patient with a history of gout can precipitate a gouty attack; warn the patient of this possibility. Antiinflammatory drugs (NSAIDs or colchicine) also are given to prevent a painful acute flare as the antihyperuricemic drug is initiated.

Side effects of allopurinol include skin rash, GI distress/diarrhea, and a potentially life-threatening hypersensitivity syndrome (see below). Decrease the dose of allopurinol in patients with chronic kidney disease and in patients taking azathioprine or mercaptopurine because metabolism of these drugs is inhibited by XOIs and can lead to increased drug toxicity such as bone marrow suppression. You do not have to adjust with mycophenolate mofetil (used often now as azathioprine substitute).

Be aware that < 2% of allopurinol users can develop a potentially fatal hypersensitivity reaction that presents with fever, acute kidney injury, eosinophilia, liver dysfunction, and a rash. Patients more likely to develop this adverse reaction are those with decreased renal function who are given allopurinol and a diuretic.

Febuxostat is associated with rash, elevated LFTs, and arthralgias. You do not have to dose-adjust for a glomerular filtration rate above 30 cc/min. Do not use this drug with azathioprine or mercaptopurine because it is a more potent XOI than allopurinol.

Low-purine diets are poorly tolerated—mostly because they are not palatable, which promotes patient nonadherence. Also, they are not very effective; lowering UA levels only ~ 1 mg/dL. The best diet is simple caloric restriction with an emphasis on complex carbohydrates (in lieu of processed simple sugars)—goal is to effect weight loss, which lowers incidence of gout. Intake of certain foods should definitely be reduced: beer (≤ two 12-oz cans/day) and distilled beverages (wine is OK), liver, and "sweetbreads" (thymus and pancreas). Sugar drinks and those containing fructose (but not diet sodas) also increase gout flares.

While not used to treat gout, you should know about the drug rasburicase. This drug infusion was approved by the FDA in 2009 for initial management of elevated UA levels in patients at risk for tumor lysis syndrome (TLS) as a result of cancer treatment. (See more about TLS in the Oncology section, Book 4.) Unlike the OIs that prevent UA production and have no effect on existing UA, rasburicase provides the enzyme uricase, which metabolizes UA to allantoin, which is very soluble and easily excreted by the kidneys.

In 2010, pegloticase was approved by the FDA for treatment of refractory tophaceous gout. Similar to rasburicase, this drug is given by infusion and metabolizes UA to allantoin. In contrast to rasburicase, pegloticase is pegylated to increase its half-life to 2 weeks (vs. 18 hours for rasburicase), making it a viable chronic

treatment. Infusion reactions, including anaphylaxis, are the main side effects. It is also contraindicated in G6PD deficiency, so patients at high risk should be screened (males of African, Mediterranean, or Asian descent).

Gout Pearls

Know!

- Low-dose aspirin interferes with urate excretion. High-dose aspirin causes uricosuria.
- Differential Dx for acute monoarticular joint swelling = crystalline vs. infection vs. fracture/trauma.
- Gout can cause fever.
- Premenopausal women rarely get gout.
- Older women may present with polyarticular pseudorheumatoid gout (gout that presents similarly to RA). So, think of gout in the older woman who looks like she has suddenly developed RA. Always look for crystals in joint fluid!
- Gouty joint radiographs may have a characteristic erosion with an overhanging edge, termed a "rat-bite" erosion that is caused by a tophus.
- RA and gout rarely coexist.
- In spite of the recommendation to ensure that a gout flare is not caused by coincident infection: Acute gout + joint infection is so rare, it could be published as a case report. The infrequency is probably secondary to the exuberant inflammatory response against the intracellular crystals.

CPPD DEPOSITION DISEASE

Calcium pyrophosphate dihydrate (CPPD) crystals cause chondrocalcinosis (calcium in the cartilage) and subsequent damage to joints. Most idiopathic CPPD deposition occurs in patients > 65 years of age and who have underlying joint damage from OA or trauma. However, when you see CPPD deposition in a patient < 50 years of age, consider these predisposing conditions:

- Primary hyperparathyroidism
- Hemochromatosis: Except in females; recognize that the monthly menstrual cycle acts as a form of phlebotomy, so women with hemochromatosis may not have a manifestation of CPPD until after menopause. Therefore, still consider this diagnosis in postmenopausal women.
- Hypothyroidism
- Hypomagnesemia
- Hypophosphatemia

The presentation ranges from asymptomatic deposition of crystals in joint cartilage (visible only on radiographs), to an acute monoarticular arthritis similar to uric acid gout, to presentations similar to OA and RA. "Chondrocalcinosis" is calcification of cartilaginous tissue and is a hint to underlying CPPD, so think of this diagnosis if you're shown obvious calcifications in the cartilage on a radiograph of a small joint. If the presentation is one of an acute arthritis, the arthrocentesis usually reveals an inflammatory joint fluid (WBCs > 2,000 cells/mm^3) with an excess of neutrophils, some of which will contain CPPD crystals.

CPPD arthropathy usually affects the knee. Other common joints affected by CPPD include wrists, MCPs, shoulders, elbows, and ankles. Recall from the OA section, we said that OA rarely involves these joints! If your patient has wrist synovitis, first think CPPD deposition—not OA! Also, when chondrocalcinosis is visible on radiographs of the wrists/hands, think CPPD.

Diagnose CPPD by finding intracellular crystals that are blunted, rhomboid, and are weakly positively birefringent under polarized light (crystals are light blue when parallel to the color compensator). See examples of intracellular and extracellular CPPD crystals in Image 6-7 and Image 6-8. Recall: Uric acid crystals are needle-like and are strongly negatively birefringent (bright yellow when parallel to the compensator). Be able to distinguish uric acid and CPPD crystals from photos (based on color) and from descriptions of the crystals.

CPPD crystals dissolve and change their birefringence when stored > 12–24 hours, so analyze the fluid immediately. Urate crystals are much less likely to dissolve. If your fluid cannot be examined within a few hours, refrigerate it to slow the decomposition of crystals and white cells.

Quick review: CPPD crystals = rhomboid, light blue when parallel, positive birefringence, chondrocalcinosis.

Treat the acute arthritis presentation with joint aspiration and NSAIDs and/or intraarticular glucocorticoid administration. Colchicine may be used but is less effective. If CPPD is caused by an underlying diagnosis, such as hemochromatosis, then treat the underlying disease.

In hemochromatosis, phlebotomy may not change the joint calcification, but other manifestations of disease, such as diabetes, can be assessed and treated.

Again, look out for the patient on the Board exam with wrist arthritis—think CPPD and screen for hemochromatosis, hyperparathyroidism, and hypothyroidism in patients younger than ~ 60 years.

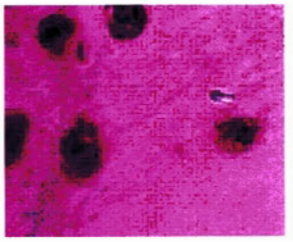


Image 6-7: CPPD crystal; Extracellular

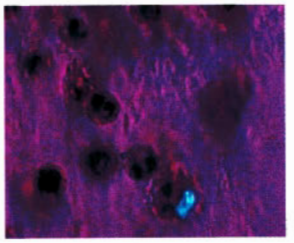


Image 6-8: CPPD crystal; Intracellular

QuickQuiz

- Synovitis of certain joints should make you think of CPPD disease. Which joints are they?
- What do CPPD crystals look like under polarized light?
- Which diseases are associated with CPPD?
- What is the typical WBC in the synovial fluid of a septic joint? Which type of WBC?
- What are common pathogens associated with septic joints?
- How do you diagnose gonorrheal synovitis?
- What is special about the approach to diagnosis of gonorrheal synovitis compared to traditional septic joint workup?

HYDROXYAPATITE ARTHROPATHY (HAA)

HAA is also known as basic calcium phosphate arthropathy or calcium apatite deposition disease. Hydroxyapatite is the primary mineral in bone and teeth. Abnormal accumulation may occur idiopathically; in hypercalcemic/hyperparathyroid states; in damaged tissues; and in scleroderma and dermatomyositis. Crystal arthropathy in dialysis patients is sometimes due to HAA, and both CPPD and HAA are associated with OA.

Think about HAA in elderly patients (especially older women) who have a very destructive arthropathy of the shoulders ("Milwaukee shoulder"), hips, knees, and/or hands with noninflammatory synovial fluid (increased mononuclear cells) and no visible crystals. Radiographs show calcification in and around the joint +/– erosions, depending on how bad the disease is.

Confirm diagnosis of HAA arthropathy with identification of the HAA crystals in the joint fluid. These crystals are very small, nonbirefringent, and can be seen only by electron microscopy or special staining using alizarin red (done by pathologists).

Treatment for acute HAA is the same as for acute CPPD. For dialysis patients, controlling serum phosphorus levels will help prevent flares.

INFECTIOUS ARTHRITIDES

SEPTIC ARTHRITIS

Bacterial/septic arthritis is usually inflammatory, monoarticular, occurs from seeding during bacteremia, and is associated with fever. In most cases, joint aspirate is inflammatory (average WBCs = 100,000 cells/mm^3) with predominance of neutrophils, and a Gram stain frequently shows the infecting organism, but not always. An indolent history with noninflammatory fluid suggests mycobacteria or fungi as etiologies, or a noninfectious cause of arthritis.

Know these septic joint associations and pearls:

- *S. aureus* = usual cause of septic joint in adults, especially in RA patients.
- Adolescents and young adults = *N. gonorrhea* (most common organism in this age group!) Remember that synovial WBC counts may be in only the 10,000 cells/mm^3 range.
- Sickle cell anemia = *Salmonella* and pneumococcus, but staph is still most common.
- Human bites = anaerobes and *Eikenella*.
- Animal bites = *Pasteurella multocida*.
- Extensive comorbidities = gram negatives, group A streptococci, pneumococcus.
- Indolent, chronic, and with noninflammatory fluid (+/– bloody) = mycobacteria, fungus, or noninfectious.
- Injection drug users = staph, strep, gram negatives (especially *Pseudomonas*); predilection for axial disease (e.g., sternoclavicular and sacroiliac joints).
- Prosthetic joints = *S. aureus* or coagulase-negative staph; "loosening of the prosthesis" is very concerning for infection.

Pregnancy and menstruation are predisposing factors for disseminated gonorrhea. Presentation is fever, migratory polyarthritis, tenosynovitis, and dermatitis (red papules that become pustular). Gonococcal joint infection is always from dissemination, but you might have missed the clinical signs/symptoms during dissemination. Remember to consider this diagnosis in the adolescent with knee pain.

In gonococcal arthritis, fluid analysis usually shows only mild inflammation (average WBCs = 10,000–20,000 cells/mm^3), and joint cultures are usually sterile. Blood cultures are positive in < 50% of cases.

Know that, in disseminated gonorrhea, you should culture all mucosal surfaces that could be harboring the organism (i.e., cervix, rectum, and oropharynx in women; urethra, rectum, and oropharynx in men; any skin lesions) in addition to the joint fluid and blood. Adequate cultures require direct plating of specimen material (e.g., joint fluid, mucosal swab, skin swab) on Thayer-Martin (chocolate) agar at the bedside. So, go to the micro lab first and get your special media before you do an arthrocentesis. Then, squirt some of the joint fluid directly onto the chocolate agar plates—in addition to sending the fluid for routine Gram stain, culture, and sensitivity. If you have the option of sending joint fluid for gonococcal PCR, do that—the results are highly sensitive.

In nongonococcal septic synovitis, the joint is hot and tender, and the patient may be febrile. Try to get your

joint fluid before any antibiotics are given. Fluid is inflammatory, and Gram stain of the joint fluid usually shows WBCs and organisms, especially if staph is the cause. Fluid cultures grow the organism most of the time, and about half the time, blood cultures are also positive. Direct inoculation of blood culture vials with joint fluid may increase the likelihood of isolating the organism, although studies are divided about whether or not direct inoculation makes a difference.

Treatment for septic arthritis includes systemic antibiotics targeted to the Gram stain result: nafcillin or vancomycin for gram-positive cocci; broader coverage for gram negatives, pneumococcus, and gonorrhea if no organisms are seen; antipseudomonal coverage if injection drug use is suspected; and repeated drainage of the joint. Joints that don't improve with antibiotics and repeated aspiration should go for laparoscopic or open lavage. Intraarticular antibiotics are not used or recommended.

Patients who have prosthetic joints but need to undergo procedures (e.g., dental, urologic) are at risk for developing transient bacteremia and seeding of their joint. Prophylaxis for procedures in these patients is controversial. The Infectious Diseases Society of America (IDSA) is writing a clinical guideline for prophylaxis of patients with prosthetic joints at the time of this writing, with expected release in the last half of 2012. IDSA clinical practice guidelines can be found at www.idsociety.org.

Acute Rheumatic Fever

Acute rheumatic fever (ARF) is the immunologic sequela of previous group A strep infection. Polyarthritis is one of the World Health Organization's criteria for diagnosis. Consider ARF in patients who develop fever and polyarthritis, especially if you see associated chorea, erythema marginatum, nodules, or evidence of carditis; e.g., prolonged PR interval.

WHIPPLE DISEASE

Whipple disease is rare and caused by the infectious agent *Tropheryma whippleii*. It predominantly affects middle-aged men (M > F [4:1]) and causes recurrent episodes of nondestructive seronegative inflammatory arthritis that predominantly affect large joints (e.g., knee). It is also commonly associated with GI manifestations including diarrhea, malabsorption, and weight loss. Fevers, constitutional symptoms, lymphadenopathy, skin hyperpigmentation, and neurologic finds are also seen. The main neurologic symptom is memory loss due to a slowly progressive dementia. "Oculomasticatory myorhythmia" is pathognomonic for Whipple disease. That's a lot of systems to remember. Basically, think about Whipple's in middle-aged men with diarrhea, fat malabsorption, and recurring episodes of inflammatory arthritis.

The diagnosis is made by finding macrophages containing periodic acid-Schiff (PAS)-positive gram-positive bacilli in tissue biopsies from any system that is involved. PCR can also be used.

Treatment usually requires parenteral antibiotics (e.g., ceftriaxone) initially to ensure CNS penetration, followed by oral therapy, such as double-strength TMP/SMX x 1–2 years! Recurrences are common.

TUBERCULOUS ARTHRITIS

Tuberculous arthritis is usually a mildly symptomatic, chronic knee effusion that persists for years. The arthritis is either an expression of primary TB or a site of reactivation, but most patients do not have associated active pulmonary TB. Remember that immunosuppressant agents, particularly anti-TNF inhibitors, are risk factors for reactivation TB.

Joint fluid is mildly inflammatory (average WBCs = 20,000 cells/mm^3). Know that acid-fast smears and cultures are useful, but their sensitivities are not great. Synovial cultures are positive in ~ 80% of people with infection.

As with pleural TB, biopsy of the synovium for pathology and culture is most helpful. (Pathology shows granulomas.)

Send the fluid for TB PCR if available at your institution—it's very sensitive. A positive TB skin test in a patient with a chronic joint effusion should make you think about (and investigate for) TB! As with pulmonary TB, TB skin tests aren't always positive in people with infection, so do not let a negative test dissuade the workup if you suspect TB based on the history or other data.

Treatment is the same as for active pulmonary TB: isoniazid, rifampin, pyrazinamide, and ethambutol x 2 months—until you get the organism and its sensitivities. Then, narrow therapy to 2 drugs x 4 more months (6 months total). Treat longer if the patient is HIV+.

VIRAL ARTHRITIS

Viral diseases can cause a true infection of the joint (aseptic arthritis) or a reactive (immunologic) arthritis (previously discussed on page 6-14).

Patients with aseptic arthritis frequently will have a pseudo-RA picture, which resolves with minimal therapy (NSAIDs) and typically does not recur.

Parvo B19 is one of the more common causes of aseptic synovitis in adults. Think about parvo B19 when you see a young adult female with school-aged children who presents with symmetric synovitis of the hands—the synovitis has been present for weeks, and she may even describe a recent "slapped cheek" and "lacy" or "reticular" rash in the children, which is how parvo

QuickQuiz

- What are presenting features of Whipple disease? The organism involved?
- Describe the presentation of tuberculous synovitis.
- How do you diagnose Lyme arthritis?

presents in the younger age group. Again, the history of exposure to sick children 1–2 weeks prior to the arthritis should alert you to the possibility of parvo as the cause of hand arthritis. The diagnosis can be confirmed by positive IgM against parvovirus B19.

Other causes of aseptic synovitis: rubella, mumps, acute HBV (oligoarthritis/arthralgias associated with maculopapular rash, fever, and urticaria before jaundice), chronic HCV, and enteroviruses.

Acute rheumatic fever (ARF) is the immunologic sequela of previous group A strep infection. Polyarthritis is one of the World Health Organization's criteria for diagnosis. Consider ARF in patients who develop fever and polyarthritis, especially if you see associated chorea, erythema marginatum, nodules, or evidence of carditis; e.g., prolonged PR interval.

Remember reactive arthritis and know that it is associated with HIV infection, as well as the many bacteria listed on page 6-14.

LYME ARTHRITIS

Lyme arthritis is a manifestation of late Lyme disease. It occurs a few months, and up to 1–2 years, after the disease-causing tick bite in 50% of untreated patients. True Lyme arthritis is an intermittent or persistent, asymmetric, monoarticular or oligoarticular arthritis, usually affecting only 1 or a small number of large joints (knee most commonly). Up to 50% of patients never have evidence of early Lyme disease (e.g., erythema migrans, carditis, cranial nerve abnormalities, peripheral neuropathies, mononeuritis multiplex, or meningoencephalitis). A small number of patients actually develop destructive, erosive arthritis. (See also the Infectious Disease section, Book 1.)

Criteria have been established for diagnosis and treatment of Lyme disease by the IDSA (initially updated in 2006; reviewed for accuracy in 2011). Diagnose Lyme arthritis using a serum ELISA test for anti-*Borrelia burgdorferi* IgG. The IgM ELISA test is not appropriate because arthritis represents a late manifestation (thus, IgG is more appropriate), and these IgM tests are often falsely positive. Do not do any further testing if the IgG ELISA test is negative; a negative test definitively excludes Lyme as the cause of arthritis.

False-positive Lyme ELISA serology can be caused by many disease states, including SLE, RA, Rocky Mountain spotted fever, other spirochetal diseases (syphilis and leptospirosis), and is seen at a high rate in healthy controls. So, order a Western blot as a confirmation test in patients with a + IgG ELISA.

Although the test is rare, DNA amplification is useful on joint fluid, but the rate of false positives is high, so do not order it unless the patient has a positive IgG ELISA and Western blot. The DNA can persist in the joint long after adequate treatment, so a positive PCR test does not identify whether disease is active or treated. Antibody tests on the joint fluid are not helpful.

Treat Lyme arthritis with a single course of oral doxycycline or amoxicillin x 28 days; then reassess, provided no neurologic involvement is present.

Persistent synovitis after oral antibiotics can be treated with NSAIDs and observation, as occasionally the inflammation of Lyme takes weeks to improve. If the patient still has synovitis after oral antibiotics and a period of observation and NSAIDs, retreatment with another 28 days of oral doxycycline or amoxicillin is appropriate. Ceftriaxone can be used for 14–28 days in patients who did not improve at all on the oral regimen.

Once Lyme arthritis has been treated with ceftriaxone x 28 days, or two regimens of oral antibiotics, the patient has been definitively treated, and any further inflammation should be treated conservatively and by a rheumatologist. Options include NSAIDs, hydroxychloroquine, and intraarticular steroids.

Know that any patient with arthritis who has symptoms of neurologic involvement (except for Bell's palsy) should undergo a lumbar puncture and be considered for treatment with intravenous ceftriaxone, instead of oral antibiotics.

Some patients receive the diagnosis of "chronic Lyme disease," but know that this diagnosis is not considered standard of care because definitive data do not exist to support chronic infection. As such, it is inappropriate to treat any form of Lyme disease with prolonged intravenous antibiotics. In very rare circumstances, a patient with late neurologic involvement may require an additional one month of parenteral ceftriaxone after the first month of treatment, but no patient should receive more than two 28-day parenteral regimens. Multiple months of parenteral antibiotics, and antibiotics that are ineffective against the organism (e.g., azithromycin, tetracycline, tinidazole, rifampin, malarone, artemisia), are not considered standard of care by the IDSA.

OTHER ARTHRITIDES

This section contains joint diseases that are associated with systemic illness—or those we are not sure how to easily characterize!

Adult Still's Disease

Adult Still's disease is an uncommon illness, although a similar disorder, called systemic-onset juvenile arthritis, is more commonly seen in children younger than 16 years. Adult Still's disease presents with a very distinctive "evanescent" (means "vanishing" or "disappearing"), macular, salmon-pink rash that coincides with a daily ("quotidian") high, spiking fever. This coincidence of a rash that appears with the fever and disappears at defervescence is a big clue to the diagnosis in practice. Include adult Still's disease in the differential diagnosis of fever of unknown origin (FUO).

Mild oligoarthritis usually develops in most patients. Joint fluid is inflammatory (average WBCs = 13,000 cells/mm^3). Other signs/symptoms include sore throat, lymphadenopathy, myalgias, arthralgias, and serositis. Some patients may progress to a destructive polyarthritis, and their joints can actually fuse (especially the wrists), but this is not common.

Associated lab abnormalities include:

- anemia of chronic inflammation (or anemia of chronic disease),
- reactive thrombocytosis,
- increased ESR or CRP,
- transaminase elevations, and
- high serum ferritin levels.

Besides the rash, a high serum ferritin level (> 10x normal) is strongly associated with this disease and correlates with more severe disease activity.

Initial treatment for mild disease includes NSAIDs, but most patients ultimately require systemic steroids. Anti-TNF agents are recommended in patients who are refractory to systemic steroids.

Hemochromatosis Arthritis

Over 40% of patients with hemochromatosis will get arthritis; in many, the arthritis is the presenting symptom of the disease. Usually this happens in patients > 50 years of age.

This arthritis affects small joints first. Think about hemochromatosis, especially when you see synovitis of the 2nd and 3rd MCPs. Next comes big joints—knees, ankles, and shoulders. The joint fluid is noninflammatory (a big clue to help you distinguish this arthritis from the inflammatory ones that also affect the MCPs, such as RA). The morning stiffness of this arthritis is also usually < 30 minutes; x-rays show narrowed joint spaces. Remember that CPPD deposition occurs in association with hemochromatosis in ~ 50% of patients with the arthritis. So you may also see chondrocalcinosis on radiographs and/or weakly positive birefringent crystals in the joint fluid.

Treating hemochromatosis with phlebotomy may help other manifestations of disease but not the arthropathy. Treat joint disease with acetaminophen and NSAIDs. Hemochromatosis can easily be screened for with iron studies. An elevated iron saturation level (iron/TIBC of > 45%) or elevated ferritin level (> 200) suggests the diagnosis.

Neuropathic Joints

We used to call these Charcot joints—joints that are destroyed via 2 proposed mechanisms:

1) Repeated trauma secondary to loss of pain sensation and/or proprioception
2) Autonomic dysfunction that leads to regional hyperemia, osteoclastic stimulation, and active bone resorption

Diabetes is the most common cause.

Joint findings are similar to very severe OA, with osteophytes, except that erosions can also occur. Bony fragments, reminiscent of the trauma, are often seen floating in the joints on radiographs. To try to repair the damage, bone becomes overgrown, and noninflammatory joint effusions develop. Eventually, the joints become unstable and lax. Think about this diagnosis in somebody with a horrific-looking joint and minimal associated pain.

Treat these with stabilization and focus on the underlying disease.

Hypertrophic Pulmonary Osteoarthropathy (HPOA)

Think about HPOA when you see a joint effusion in a smoker who also has clubbing of the fingers. HPOA can be primary or familial, but it is most often associated with lung malignancies (termed "secondary HPOA"). We don't know the mechanism for this condition, but it is associated with periosteal bone formation, joint effusions (due to synovial proliferation and inflammation), and clubbing (due to effects on connective tissue).

The bone changes can be associated with dull, aching pain that is intense when you apply pressure to the arms and legs. The arthropathy is usually slight and appears noninflammatory (effusion WBCs < 500 cells/mm^3). Hands are usually not part of this presentation, other than clubbing!

In early stages, radiographs show periosteal bone growth adjacent to radiolucencies, especially in the diaphyses. Later, irregular cortical thickening appears, mostly over

QuickQuiz

- What are the features of adult Still's disease?
- Does hemochromatosis initially affect large or small joints?
- Characterize the typical patient who develops primary Raynaud's.
- Characterize the pattern of synovitis in systemic lupus.
- What are the patterns of skin rashes in lupus?

metaphyses. Use imaging to look for an intrathoracic malignancy, especially lung cancer. Infectious etiologies are also seen in this syndrome, including bronchiectasis, lung abscess, and TB. If the cause is a lung infection, the arthropathy and clubbing usually disappear after antibiotics.

Remember: The triad of clubbing, polyarthritis, and lung cancer = HPOA.

CONNECTIVE TISSUE DISEASE

RAYNAUD PHENOMENON

Primary (idiopathic) Raynaud phenomenon usually begins in young women within a few years following menarche and is not associated with any rheumatologic disease. In ~ 90% of young women with Raynaud's, the condition is primary. Primary Raynaud's sometimes is associated with livedo reticularis.

Secondary Raynaud's is typically more severe and occurs in many connective tissue diseases and with certain prescription and illegal drugs. It is usually present in most scleroderma patients, but it's also seen frequently in RA, SLE, Sjögren's, MCTD, PBC, and occasionally dermatomyositis. Common drugs that may cause Raynaud's include beta-blockers, ergots, clonidine, cocaine, and methamphetamines.

Raynaud syndrome is defined as a tricolor change of the fingers and/or toes that occurs as a result of vasoconstriction when exposed to cold or stress—even the stress of going to the doctor can elicit the response in some patients (Image 6-9). Fingers and/or toes turn white (blanching), then blue (cyanotic) as the hemoglobin deoxygenates, then red (erythematous) as the vessels dilate with warmth or de-stressing. Paresthesias and clumsiness may be associated with the vasospasm episode. Fingertip ulcerations are an indicator of associated rheumatologic disease, because ulcerations rarely occur in primary Raynaud syndrome.

Any of the following suggest the patient has secondary Raynaud phenomenon: male, age > 40, asymmetry of findings, fingertip ulcerations, and coexistent vascular or autoimmune disease.

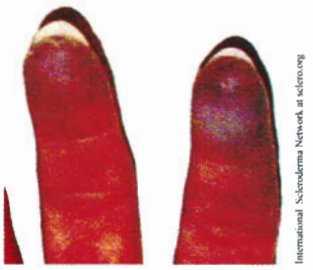


Image 6-9: Raynaud syndrome

Treatment includes avoiding the cold and the use of drugs that can exacerbate vasoconstriction. Calcium channel blockers, alpha-blockers, and transdermal nitroglycerin are effective. Localized digital sympathectomy should be limited to patients who have failed medical treatment and continue to experience ischemia or are at risk of losing a digit.

SYSTEMIC LUPUS ERYTHEMATOSUS

Manifestations of Systemic Lupus

Overview

Systemic lupus erythematosus (SLE) is the prototypic autoimmune disease. It ranges from mild rash, arthralgias, and fatigue to severe, life-threatening manifestations. SLE is present more often in females than males and is most prevalent in African-Americans. Most patients are diagnosed between ages 14 and 65 years. Manifestations can occur in virtually any part of the body.

SLE: Joints

Lupus arthritis is inflammatory, symmetric, nonerosive and polyarticular, usually including the small joints of the hands and wrists and the knees (Image 6-10). Recall that rheumatoid arthritis is also inflammatory, symmetric, and polyarticular, but it is erosive.

SLE: Skin and Mucocutaneous Rashes

Classification of lupus rashes:

- **Discoid**: hyperpigmented edges, which may be raised, frequently causing central scarring with destruction of melanocytes and hair follicles. Many patients with SLE also have discoid rashes, but patients with discoid lupus have only a 5–10% chance of developing SLE (Image 6-11 and Image 6-12).
- **Systemic**: erythematous, ultraviolet light-sensitive (occurs whether weather is cloudy or sunny); concentrated on malar area ("butterfly" that spares nasolabial fold; Image 6-13), neck, ears, upper extremities, and back that flares with systemic disease.
- **Subacute cutaneous**: ultraviolet light-sensitive, psoriatic-like. Patients can have negative ANAs with +Ro/La. Rash is often associated with systemic lupus, but not always.

- "**Other**": lots of other rashes (e.g., urticaria, vesicles, lichen planus).

Alopecia is common, as well as nonpainful, aphthous-like ulcers on mucosa of the nasopharynx.

Raynaud phenomenon in the hands and feet is not uncommon. See previous topic for more extensive discussion on Raynaud's.

SLE: Lung

Pleuritic chest pain +/– effusion (most common), alveolar infiltrates, pneumonitis (with subsequent fibrosis and pulmonary arterial hypertension), and alveolar hemorrhage—a medical emergency.

SLE: Heart

Pericarditis (most common), myocarditis, valvular lesions (termed "Libman-Sacks endocarditis" = thickening, nodules and sterile vegetations related to antiphospholipid antibodies), and premature coronary heart disease. The Framingham Offspring Study revealed that women ages 35–44 with SLE have a 50-fold increase in myocardial infarctions.

SLE: Kidney

Glomerulonephritis is the manifestation of SLE with the most morbidity and, along with infection, is a major cause of mortality in these patients. The presence of anti-dsDNA is associated with eventual nephritis.

African-American lupus patients are more likely than Caucasians to develop aggressive renal disease. Once lupus nephritis develops, lifetime recurrences are likely.

"Bad" kidney disease (advanced classifications) is associated with an active urine sediment: proteinuria (usually > 500 mg/day) and microscopic hematuria, as well as a high titer of anti-dsDNA. Always check a U/A on any patient whom you suspect has systemic lupus.

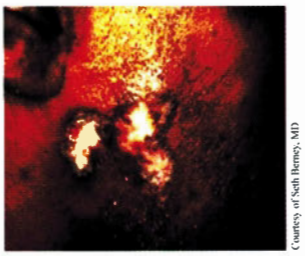


Image 6-11: Discoid lupus

Image 6-12: Discoid lupus

Kidney disease is staged by the International Society of Nephrology (ISN) and the Renal Pathology Society (RPS). These classifications organize glomerular disease, but know that systemic lupus can also affect the tubules and vasculature.

ISN/RPS classification (treatment) of glomerulonephritis in SLE:

- Class I: Minimal mesangial (no treatment generally needed)
- Class II: Mesangial proliferative (+/– glucocorticoids)
- Class III: Focal; ≤ 50% of glomeruli (glucocorticoids and cytotoxics)
- Class IV: Diffuse (glucocorticoids and cytotoxics)
- Class V: Membranous (glucocorticoids)
- Class VI: Advanced sclerotic; ≥ 90% sclerotic glomeruli (disease irreversible)

Combinations of the above stages may occur. The letters "A" and "C" are also listed as subcategories to reflect whether the changes are "active" or "chronic."

Important: Treat class III and IV disease with cytotoxics and corticosteroids to prevent end-stage kidney disease, which develops within 2 years in untreated patients.

Image 6-10: Symmetric polyarthritis of SLE

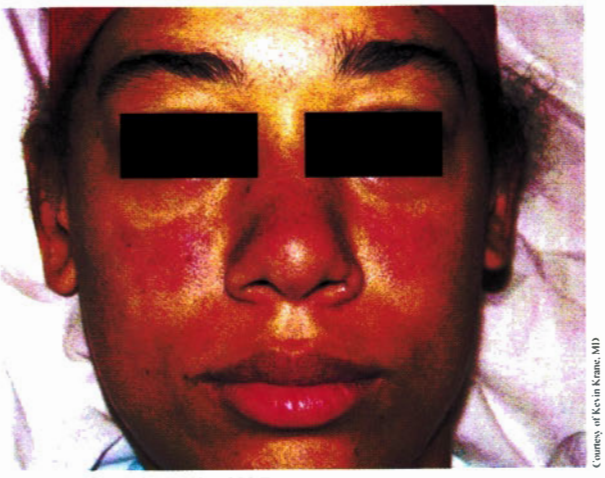


Image 6-13: Malar rash of SLE

QuickQuiz

- What is the increase in risk of myocardial infarctions in women with SLE?
- Which autoantibodies are associated with development of lupus nephritis?
- What classifications of SLE kidney disease require treatment with cytotoxics?
- What hematologic changes in systemic lupus are in the criteria for diagnosis? (See Table 6-7.)

SLE: Blood

Anemia of inflammation (most common), leukopenia (specifically lymphopenia), thrombosis (due to anti-phospholipid antibody syndrome), thrombocytopenia, idiopathic thrombocytopenic purpura, and Coombs + hemolytic anemia with reticulocytosis—sometimes microangiopathic and associated with thrombotic thrombocytopenic purpura (more in the Hematology section, Book 4).

SLE: CNS

Cognitive/behavioral changes (most common), psychosis, aseptic meningitis, organic brain syndrome, seizures, chorea, and strokes occur with SLE. Even severe abnormalities may clear rapidly with regression of disease. Spinal fluid may be normal, even with severe symptoms; but you may find elevated protein or WBCs (mostly lymphocytes), especially in cerebritis. MRI of the brain may show scattered areas of increased intensity, suggesting a vasculopathy.

Evaluate all SLE patients for infection, including lumbar puncture, particularly if immunosuppressed. Know that anti-Sm is associated with CNS disease and that antiribosomal P protein is associated with psychosis.

Diagnosis

SLE can be diagnosed by signs and symptoms alone with high sensitivity and specificity (Table 6-7).

The ANA is the most sensitive test for SLE (99% of patients with active disease have a positive test), but it has very poor specificity and can be positive even in patients without disease. Among the subtypes of ANA, anti-dsDNA and anti-Sm in high titers are very specific (usually negative in patients without disease; i.e., rarely false positive), but they are not very sensitive. Sometimes they are negative in patients with true disease; i.e., false negative. Never check anti-single–stranded DNA. It's worthless and occurs in many illnesses.

Patients with active SLE usually have low levels of C3 and C4. So, in working up a case of possible SLE, first do an ANA. If the ANA is positive, do an ANA profile. Current ANA testing uses a human cell line (HEp-2 cells) as the substrate and rarely produces a false-negative test. So a negative ANA basically excludes systemic lupus. Very rarely a person will meet criteria for systemic lupus and be ANA-negative (0.14%). ANA-negative SLE patients usually are SSA (Ro) positive. This is important for 3 reasons:

1) SSA (Ro)/SSB (La) antibodies are associated with neonatal lupus and congenital heart block. General internists need to know about this risk when counseling women with lupus about pregnancy.
2) SSA and SSB are the only appropriate autoantibodies to order in an ANA-negative SLE patient.
3) Subacute cutaneous lupus may also be ANA– and Ro/La+.

SLE and Pregnancy

Lupus patients have a higher incidence of failed pregnancies. Pregnancy is not advised until disease has been quiescent for six months or longer. Risk of pregnancy complications (flares or fetal problems) is much greater if disease is active (especially renal manifestations) or if the mother has anti-dsDNA or

Table 6-7: Diagnostic Criteria for SLE

4 or more or the following during course of the disease. 95% specificity, 75% sensitivity.

Mucocutaneous (4)	1)	Rash with UV exposure
	2)	Malar rash
	3)	Oral and nasopharyngeal ulcers
	4)	Discoid rash (scaly, round patches)
Organ Systems (5)	5)	Arthritis (symmetric, nonerosive, ≥ 2 joints)
	6)	Serositis (pleurisy or pericarditis)
	7)	Renal (proteinuria or cellular casts)
	8)	Blood changes (hemolytic anemia, leukopenia [or lymphopenia], thrombocytopenia)
	9)	Neuropsychiatric features (seizures or psychosis)
Lab Values (2)	10)	Anti-dsDNA, anti-Sm, or APS
	11)	Positive ANA

antiphospholipid antibodies. Favorable pregnancy outcomes are associated with quiescent disease, minimal medical therapy, and medications that can be continued during pregnancy (e.g., prednisone, hydroxychloroquine, and azathioprine). Pregnant women with antiphospholipid syndrome (APS) and a history of recurrent miscarriages can be treated with heparins (low-molecular-weight or unfractionated) plus low-dose aspirin to decrease the incidence of miscarriage. Heart block starting as early as the 2nd trimester may present in fetuses/infants of mothers with SLE who have SSA (Ro) and SSB (La) antibodies (Table 6-1 on page 6-2). For these patients, begin serial fetal echocardiograms at about 16–18 weeks gestation.

If a SLE patient wishes to become pregnant and has had a recent lupus flare, continue the glucocorticoids. Measure baseline complements, anti-dsDNA, SSA/SSB, and a 24-hour urine protein before or very early in the pregnancy. Manage flares during pregnancy with glucocorticoids. Refer pregnant women with systemic lupus to a high-risk obstetrician (and pediatric cardiologist, if appropriate).

Prognosis

10-year survival of systemic lupus is ~ 90% if patients receive optimal treatment. Elevated anti-dsDNA and low complement levels indicate worse prognosis, with increased risk for nephritis. Elevated anti-U1RNP in the setting of a high-titer ANA and negative anti-Smith may indicate a better prognosis, because the disease may actually be mixed connective tissue disease (MCTD) and not SLE. Patients with SLE are also at higher risk for infections (due to immunosuppression), malignancy (especially hematologic ones), osteoporosis (secondary to glucocorticoids), and premature death from CAD (from disease inflammation and glucocorticoids).

Treatment of SLE

Stress exacerbates SLE. Avoid surgery during active disease and encourage sunscreen to protect against the ultraviolet-sensitive rash. Start with NSAIDs for joint disease. (Remember, lupus arthritis is nonerosive.) Hydroxychloroquine is effective for treating skin rashes and arthritis, and it can also help prevent disease flares.

Use high-dose glucocorticoids only for patients with severe disease and major organ involvement. Fatigue and alopecia may improve as well. Low-dose maintenance corticosteroids (< 10 mg daily or every other day) are frequently required to control symptoms and prevent flares. Remember: Up to 1/3 of SLE patients on chronic high-dose glucocorticoids develop avascular necrosis of the hip/knee/humerus!

Cytotoxics (azathioprine, mycophenolate mofetil, or cyclophosphamide) are added to corticosteroids for serious flares of SLE, particularly renal and CNS disease. Cyclophosphamide and corticosteroids improve survival in patients with SLE and class III or IV glomerulonephritis.

Anti-B-cell drugs are occasionally used in patients with disease that is refractory to corticosteroids, hydroxychloroquine, and cytotoxics (e.g., rituximab and belimumab). Rituximab is a monoclonal antibody, and belimumab, approved in 2011, is an antibody directed against the B-lymphocyte stimulator (BLyS) protein. It decreases the amount of abnormal B cells, which are hypothesized to be a mechanism of action in lupus. Specific use of these drugs is very specialized.

DRUG-INDUCED LUPUS

Classic drug-induced lupus can be caused by procainamide, hydralazine, chlorpromazine, propylthiouracil, phenytoin, minocycline, and TNF inhibitors. Think about drug-induced lupus in any patient who develops constitutional symptoms (fever, arthralgias), serositis, and/or rash while taking any of the above drugs (lots of others, too). There is usually no kidney or CNS involvement. ANA is positive and anti-histone antibody is usually positive. C3 and C4 usually are normal, and anti-dsDNA is rarely positive.

Drug-induced lupus can be a tough diagnosis to make. Ideally, you find:

- a positive ANA with anti-histone antibodies, and
- a history of exposure to one of the above drugs.

Sometimes you confirm the diagnosis only in retrospect by observing complete resolution of symptoms after discontinuing the drug.

Treatment: Symptoms usually resolve within 4–8 weeks after stopping the offending agent, but the ANA may remain positive for months. NSAIDs and antimalarials may be useful. Corticosteroids work well but are only occasionally needed.

MIXED CONNECTIVE TISSUE DISEASE (MCTD)

These patients have signs of several diseases, including SLE, polymyositis, and systemic sclerosis—but mixed together. MCTD typically presents with arthritis/arthralgias and Raynaud phenomenon. The patient may present with a mild myositis and/or serositis, as well as "swollen hands." Interstitial lung disease may be the most severe complication. This disorder predominantly affects women (9:1).

Anti-U1RNP is the autoantibody to remember. High titers are associated with MCTD. Although SLE may also have anti-U1RNP, MCTD usually does not have antibodies against dsDNA, Smith, SSA (Ro), or SSB (La).

QuickQuiz

- A pregnant woman with SLE has SSA (Ro) and SSB (La) antibodies. What abnormality can occur in her fetus?
- What are potential complications of chronic corticosteroid treatment in patients with lupus?
- Which drugs are associated with drug-induced lupus?
- How does drug-induced lupus differ from systemic lupus?
- Mixed connective tissue disease has features of which diseases?
- What are the features of antiphospholipid antibody syndrome?

Patients respond well to glucocorticoids and have a good prognosis. Only rarely do they get heart failure from myocarditis or severe pulmonary hypertension.

APS SYNDROME

The antiphospholipid syndrome (APS) is characterized by vascular events and one or more autoantibodies. APS can be primary and idiopathic, or it can be secondary and associated with another disease (usually SLE), drugs, or an infection.

Vascular events that characterize APS include:

- Venous and/or arterial clots, especially those that contribute to pregnancy morbidity (e.g., stroke, deep venous thrombosis and/or pulmonary embolism)
- Miscarriage of a normal fetus at ≥ 10-weeks gestation
- Birth of 1 or more premature babies at < 34-weeks gestation because of eclampsia/ preeclampsia/ placental insufficiency
- Multiple miscarriages at < 10-weeks gestation

While not included as criteria for diagnosis, other exam findings are seen with APS:

- Livedo reticularis (Image 6-14)
- Sterile cardiac vegetations
- Thrombocytopenia
- Prolongation of the partial thromboplastin time (PTT) that is not corrected by adding 1:1 mix of normal plasma (See Hematology section, Book 4, for more information on the mixing study, which distinguishes APS from a clotting factor deficiency.)

Despite the abnormal bleeding tests, patients with APS are hypercoagulable rather than anticoagulated—because the lupus anticoagulant-associated prolonged PTT is only an *in vitro* effect.

Types of antibodies include lupus anticoagulants, anticardiolipin antibodies, and anti-β-2 glycoprotein-1. The anticardiolipin antibodies can be IgG, IgM, or rarely, IgA. β-2 glycoprotein-1 is the cofactor necessary for activity of the anticardiolipin antibodies; some patients with APS have only anti-β-2-glycoprotein-1 antibodies. Because other conditions can be transiently associated with AP antibodies, but not the syndrome, the antibodies must be present on 2 separate occasions at least 12 weeks apart for diagnosis of APS.

Catastrophic APS is a rare variant that carries a 50% mortality and manifests as multiorgan dysfunction secondary to numerous thromboses. Treatment includes anticoagulation, glucocorticoids, and plasma exchange.

Acute treatment of APS: Acute clots are treated with anticoagulation, usually low-molecular-weight heparin.

Chronic treatment of APS: Treat the underlying disease, if APS is secondary. Anticoagulation is usually given. Lifelong anticoagulation is used to treat primary disease. Warfarin is given to maintain the INR 2.0–3.0.

SJÖGREN SYNDROME

Sjögren syndrome is caused by a CD4+ T-cell lymphocytic infiltrate that destroys the lacrimal and salivary glands, resulting in decreased secretions from these glands.

Primary Sjögren syndrome (not associated with a concurrent rheumatologic disease) occurs commonly in older women who present with sicca complex (dry eyes and dry mouth) along with parotitis and adenopathy. Some patients have purpura and interstitial nephritis (with RTA), which resembles SLE clinically, but not serologically. 90% are RF+, and 70% have a positive ANA. SSA (Ro) is positive in 65%, and SSB (La) is positive in 40%. Note: SSA antigen may be present without SSB; however, it is rare to find SSB antigen alone without also having SSA.

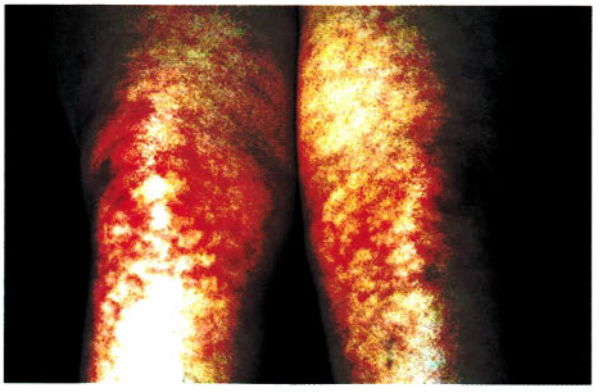


Image 6-14: Livedo reticularis

Sjögren syndrome may occur as a secondary phenomenon with any of the connective tissue diseases (RA, SLE, polymyositis, and systemic sclerosis) and can be associated with the same autoantibodies. There is an association with DR3 (as seen in SLE and occasionally in polymyositis).

There is a > 40x normal increase in risk of lymphoma with Sjögren syndrome! Close attention to dental care is paramount because these patients are at high risk for dental caries and extractions. Also, remember that children born to mothers with anti-Ro and anti-La antibodies (especially anti-Ro) are at risk for congenital heart block.

There is no set strategy for diagnosing Sjögren syndrome. In general, typical protocols include assessing the history for xerostomia (dry mouth) and xerophthalmia (dry eyes); checking for autoantibodies; and performing a biopsy of minor salivary glands. Xerophthalmia is diagnosed with a positive Schirmer test: < 5 mm of wetting in 5 minutes (normal result is ~ 15 mm).

Treatment of Sjögren syndrome is symptomatic: wetting agents, pilocarpine tablets, and punctal plugs for the eyes. Corticosteroids and other immunosuppressants have never changed the sicca symptoms in patients with Sjögren's, so use is reserved for patients who have extraglandular disease; e.g., peripheral neuropathy or lupus-like features. Antimalarial agents can help with the arthralgias, fatigue, and rashes.

SYSTEMIC SCLEROSIS / SCLERODERMA

OVERVIEW

Scleroderma is the term used to describe shiny, hard, thickened skin. Scleroderma may occur alone, but when the sclerosis involves internal organs, it is called "systemic scleroderma or systemic sclerosis" (SSc). We will focus on SSc.

SSc can be diffuse or limited in its expression—hence the names "diffuse SSc" and "limited SSc."

ANA is positive in ≥ 95% of those with SSc.

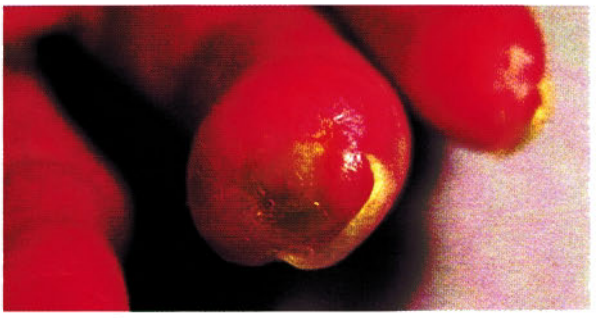


Image 6-15: Calcinosis of the fingertips

TYPES OF SYSTEMIC SCLEROSIS

Diffuse SSc

Diffuse SSc causes diffuse skin thickening and is more likely than limited SSc to have multiorgan involvement. 30% of patients with diffuse SSc are anti-topoisomerase I (anti-Scl-70) antibody-positive, and the antibody is associated with development of interstitial lung disease and reduced survival. Diffuse SSc has a wide range of presentations based on what organs are affected. Scleroderma renal crisis (SRC) is a medical emergency and almost exclusively occurs in diffuse SSc.

Limited SSc

Limited SSc causes skin thickening distal to the elbows and knees, but can affect the face and neck. It affects the internal organs to varying degrees. CREST syndrome is a subset of limited SSc. Its key features are well described by the acronym "CREST" so you can still use it as a mnemonic:

- C = Calcinosis cutis (Image 6-15)
- R = Raynaud phenomenon
- E = Esophageal dysmotility
- S = Sclerodactyly
- T = Telangiectasias (Image 6-16)

Anti-centromere antibody (ACA) is very specific for limited SSc. Pulmonary hypertension occurs in limited scleroderma (10%), especially in those who are ACA+. Interstitial lung disease usually does not occur in limited SSc (good candidate for a Board question).

Systemic Sclerosis Sine Scleroderma

This form of systemic sclerosis affects about 1% of patients. It is characterized by visceral disease without skin involvement.

MANIFESTATIONS OF SSc

SSc: Skin

Skin changes follow a progression of mucinous edema, then induration, and finally fibrosis and atrophy.

Limited SSc typically involves the distal extremities and face.

Raynaud's will eventually occur in almost all patients with both limited and diffuse types of SSc, and severe vasoconstriction may be associated with digital tip ulcerations, osteomyelitis, and black fingertips. Acroosteolysis

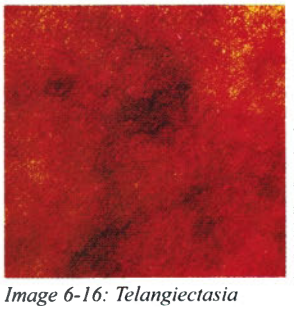


Image 6-16: Telangiectasia

Quick Quiz

- Sjögren patients are at increased risk for developing what other disease?
- Which autoantibodies are associated with diffuse scleroderma? What complication are the antibodies associated with?
- What are the key features of limited scleroderma?
- Abnormal nailfold capillaries are more commonly seen in which autoimmune disease?
- What lung manifestation is often the cause of death in patients with diffuse scleroderma?

subsequently develops. In limited SSc, Raynaud's usually occurs first—several years before other manifestations, but in diffuse SSc, the Raynaud's usually occurs at the time of other manifestations. See page 6-25 for more extensive discussion on Raynaud's.

Telangiectasias (the T in CREST) occur in diffuse SSc but are much more likely in limited SSc (Image 6-16).

Diffuse SSc skin changes characteristically involve entire extremities, chest, abdomen, and face.

Sclerodactyly is the term used to describe localized scleroderma of the fingers or toes (either type).

Abnormal nailfold capillaries may occur in either type of SSc. These capillaries reduce in number, with the remaining enlarged capillaries forming visible giant loops. These are important because there is a direct correlation between degree of abnormality of the nailfold capillaries and severity of the SSc.

SSc: Joints

Patients with SSc can have a mild, symmetric (like RA and SLE) hand stiffness +/– synovitis, but it rarely involves the hand joints (unlike RA and SLE). Patients with diffuse SSc can have a tendon friction rub, such as at the elbow, which is considered pathognomonic for SSc.

SSc: Muscles

Patients have mild muscle pain and weakness along with mild CPK elevations. Occasionally, there are features similar to polymyositis ("overlap syndrome")—or, the mild CPK elevation may be due to muscle atrophy from disuse, secondary to the skin tightness.

SSc: Lungs

Lung disease is the main cause of morbidity and mortality in SSc. Cause of death in SSc is often pulmonary hypertension from 1 of 2 causes:

1) Intimal proliferation without interstitial or alveolar inflammation (especially in anti-centromere+, limited SSc)
2) Secondary to alveolitis and pulmonary fibrosis (especially in antitopoisomerase + [anti-Scl-70+], diffuse SSc)

Cyclophosphamide may be used for interstitial lung disease.

Pulmonary hypertension may be treated with drugs that cause vasodilation of the pulmonary vasculature such as prostaglandins, bosentan, sildenafil, and/or inhaled iloprost.

Lung transplant is occasionally a viable option for lung disease in scleroderma patients.

For reasons that are not well understood, patients are at increased risk for lung cancers, especially if they smoke.

SSc: Kidney

Diffuse SSc only: Before ACE inhibitors, scleroderma renal crisis was the major cause of morbidity and mortality. Renal crisis presents within the first 5 years of diffuse disease, is associated with prior or current glucocorticoid use, and is marked by its acuity. Patients develop acute malignant hypertension and renal failure with an active urine sediment. Always consider the diagnosis of diffuse systemic sclerosis in a young female who presents with acute malignant hypertension and renal failure. Patients may even present with thrombocytopenia and a microangiopathic hemolytic anemia, as if they have thrombotic thrombocytopenic purpura (TTP).

ACE inhibitors are started early and are useful even if renal failure develops—because renal failure may be reversed with their use.

SSc: GI

Diffuse SSc only: Wide-mouthed diverticula are pathognomonic of diffuse SSc, but not limited disease.

Limited SSc only: associated with primary biliary cirrhosis (PBC) and positive anti-mitochondrial antibody.

Both diffuse and limited SSc: Dysmotility throughout the GI tract, but especially esophagus (the E in CREST) and stomach (gastroparesis) are problematic for patients with limited or diffuse SSc. Also, as the disease progresses, the lower esophageal sphincter relaxes, so patients develop severe GERD with a propensity for chronic esophagitis, strictures, and Barrett's. Proton pump

inhibitors are used in symptomatic patients. Prokinetic agents, like erythromycin, may also be helpful.

Mucosal telangiectasias may be present throughout the GI tract. Telangiectasias in the stomach can lead to bleeding and iron-deficiency anemia. This syndrome is call gastric antral vascular ectasia (GAVE) or "watermelon stomach" because of its endoscopic appearance.

Dysphagia, constipation, intestinal pseudo-obstruction, and malabsorption are also seen in both.

SSc: Heart

Cardiac involvement is common in SSc, and symptomatic disease portends a poor prognosis. Heart findings include cor pulmonale, restrictive pericardial disease, and conduction defects/arrhythmias. The majority of patients have reperfusion defects on thallium stress tests, but true coronary artery disease is frequently absent. The abnormal stress result is presumed to be due to episodic vasospasm. Diastolic dysfunction is common.

TREATMENT

Treatment is generally symptomatic and organ-specific, as reviewed above. No medicines change the course of scleroderma.

Localized skin disease can be treated with ultraviolet light therapy.

For patients with systemic sclerosis, cyclophosphamide is now being used in patients with diffuse disease and early pulmonary involvement.

Screen SSc patients for pulmonary arterial hypertension with an echocardiogram so you can catch it early. Have a low threshold to evaluate the patient for ILD with a high resolution CT scan and/or PFTS, especially in those with anti-topoisomerase I (anti-Scl-70) antibody positivity. Steroids and an immunosuppressant usually are given to treat alveolitis. Bosentan, sildenafil, or the prostacyclin analogs (e.g., epoprostenol) are options for pulmonary hypertension. Some patients require a lung transplant.

Patients with diffuse disease should monitor their blood pressure monthly. Every 3 months, check the urine protein:creatinine ratio and estimate glomerular filtration rate (GFR). Proteinuria and a > 20% reduction in GFR predicts renal crisis. Prescription for an ACE inhibitor or ARB should be given as soon as the blood pressure changes so as to prevent renal crisis. Also, remember that corticosteroids are associated with the development of renal crisis, so they should be avoided in most circumstances (except alveolitis).

Limited SSc has a better prognosis than diffuse. But remember that these patients can get pulmonary hypertension, and severely elevated pulmonary arterial pressures are associated with increased risk of death.

Diffuse SSc usually rises to a pinnacle within the first 5 years, after which no new organ systems are affected (although the organ systems that were initially affected continue to deteriorate). After this first explosion of disease, the skin usually begins to atrophy and loosen up, except for the hands. Know that the extent of skin disease in diffuse SSc is a surrogate marker for the severity of visceral disease. If renal crisis is going to happen, it usually occurs within the first 4 years of disease.

EOSINOPHILIC FASCIITIS

Eosinophilic fasciitis (EF) causes both scleroderma-like and nonscleroderma-like skin changes in the extremities—often sparing the hands (typically without Raynaud's, or a positive ANA). EF can follow unaccustomed rigorous exercise or be paraneoplastic (e.g., lymphoma, myeloma).

Tender, migrating edema of the extremities or a polyarthritis of the hands may be present in some patients.

The absence of a positive ANA, Raynaud's, and the presence of preceding vigorous exercise are 3 useful bits to help you distinguish this SSc mimic from true SSc.

Nailfold capillaries are normal. The nonscleroderma-like skin changes include peau d'orange-type induration (a late feature due to thickening and tethering of the fascial layers), which often occurs on the proximal forearms and upper legs but not the distal extremities. The affected areas have a characteristic "woody" consistency on palpation.

Also unlike SSc, most patients have a peripheral eosinophilia, which appears early in the disease course, and an increased sedimentation rate. A skin biopsy shows an eosinophilic infiltrate. ANA and RF tests are negative.

Eosinophilic fasciitis is occasionally self-limited, but most patients require moderate-dose corticosteroids (40 mg/day) or steroid-sparing agents (MTX).

INFLAMMATORY MYOSITIS DISEASES

POLYMYOSITIS AND DERMATOMYOSITIS

Overview

Inflammatory diseases of skeletal muscle include dermatomyositis and polymyositis (about equal occurrence), as well as some less-common disorders, such as inclusion body myositis. In 1975, Bohan and Peter divided myositis into the following classification, which is commonly used today:

QuickQuiz

- Compare and contrast polymyositis and dermatomyositis.

1) Polymyositis (PM; adult)
2) Dermatomyositis (DM; adult)
3) Myositis associated with malignancy
4) Childhood polymyositis or dermatomyositis
5) Myositis associated with connective tissue disease (SLE, SSc, MCDT)

Polymyositis

Features of polymyositis (PM) may be found in patients with other autoimmune disorders, such as SLE and MCTD. It is occasionally associated with the Class II HLA antigen DR3.

PM manifests as proximal muscle weakness and, in some patients, mild myalgias. PM (and dermatomyositis) typically does not cause neuropathy, only myopathy. Weakness usually occurs first in the proximal muscles (legs > arms) and mimics muscular dystrophy. These patients may present with difficulty rising from a squatting or kneeling position. Remember: Myositis generally presents with weakness, not pain! This is an important feature in distinguishing myositis from polymyalgia rheumatica, which presents primarily as muscle pain. Know how to distinguish between these two entities!

As PM progresses, dysphagia (from tongue, pharynx and upper esophageal dysfunction), dysphonia, dyspnea (from diaphragm weakness), and cardiac/ECG changes (from myocarditis or CAD) can occur, mandating hospitalization and aggressive immunosuppressive therapy.

Dermatomyositis

Dermatomyositis (DM) is similar to PM in its presentation of weakness, but skin involvement also occurs. In some patients, the skin manifestations may be quite severe—or even the sole area of involvement (amyopathic dermatomyositis).

Skin changes in DM: consist of a moderate-to-deep, purple-red, papular, sometimes scaly, photosensitive rash that occurs on the face, neck (V sign or shawl sign), and extensor surfaces of the joints. There is an associated periorbital edema with a "heliotrope" rash (Image 6-17). This rash is violaceous and classically appears on the upper eyelids, but it also may appear on the cheeks and forehead (SLE's butterfly rash does not involve the eyelids). Gottron papules are flat-surfaced, reddish-to-violet, scaling papules on the knuckles (these actually look more like "cigarette-paper" crinkling of the skin over the MCPs), and these are the most specific indication of DM (Image 6-18). Vasculitic lesions can develop, more commonly on the extremities. A psoriatic rash can appear on the scalp. Changes in nail bed capillaries are not uncommon in DM (also seen with scleroderma and SLE).

Image 6-17: Heliotrope rash

Antisynthetase Syndrome

Antisynthetase syndrome is a specific presentation of PM or DM that is characterized by very acute onset of disease, fevers and weight loss, Raynaud phenomenon, cracking and discoloration of the hands (termed "mechanic's hands"), polyarticular and nonerosive arthritis, and a predilection for interstitial lung disease. Anti-Jo-1 antibodies (a type of antisynthetase antibody) are often found with this presentation. The interstitial lung disease often is more significant than the myositis.

Diagnosis of PM and DM

The following findings help establish the diagnosis of PM and DM:

1) In 95% of patients, increased CPK with numbers in the thousands (not hundreds); you also may see an increase in other muscle enzymes, such as aldolase, LDH, AST, ALT.

Image 6-18: Gottron papules

2) + ANA (usually present in 80%) ± myositis-specific autoantibodies (e.g., anti-Jo-1, anti-SRP, and anti-Mi-2); other autoantibodies (anti-Ro, -La, -Sm, -RNP) suggest that the diagnosis is not PM or DM, but another connective tissue disorder (e.g., scleroderma, SLE, MCTD, or overlap syndrome).
3) Abnormal, myopathic EMG (increased fibrillations, decreased amplitude, and spontaneous repetitive activity) with early recruitment.
4) Abnormal muscle biopsy (gold standard); increase the yield on biopsy by targeting an involved muscle, or by using MRI to select an optimal site. Avoid biopsy of sites recently studied by EMG; instead use the contralateral side.
5) Skin biopsy in DM: biopsy of the Gottron papules or erythroderma associated with the Shawl sign; may make diagnosis and avoid need for muscle biopsy. Light microscopy and immunofluorescence show abnormalities at dermal-epidermal junction.

Cancer in PM and DM

Cancer is present in adults in 7–10% of PM and 15–20% of DM patients at the time of, or soon after, diagnosis of the muscle disease. There is no increased cancer risk in juvenile dermatomyositis. The risk increases with age, up to ~ 30–40%, in patients > 65 years of age. The patient with cancer is usually older than 50 years and has dermatomyositis more often than polymyositis. However, every patient who is newly diagnosed with either PM or DM must be evaluated for underlying malignancy with age-appropriate cancer screening, unless something in the H&P suggests a specific cancer or location to image. Current data do not support total body CT as a screen for cancer in newly diagnosed PM/DM.

Treatment of PM and DM

Polymyositis and dermatomyositis are typically treated with a high-dose prednisone, slowly tapered over 1 year, depending on response to treatment. 80% begin to respond within a few days to 6 weeks.

Patients with life-threatening manifestations usually receive intravenous pulse glucocorticoids. Azathioprine or methotrexate can be started with the steroids, so the patient can transition to a steroid-sparing regimen, eventually.

Antimalarials, such as hydroxychloroquine, are helpful for the rash in dermatomyositis. IV gamma-globulin may be effective in patients who do not respond to the other medications. Trials are examining the effectiveness of rituximab in the treatment of myositis.

Every adult patient should have cancer screening performed; if there is a poor response to treatment, reassess for cancer!

Important points on steroid use:

- Remember to prescribe vitamin D, calcium, and bisphosphonate therapy for those on chronic glucocorticoids (all patients, not just those with PM/DM).
- Think about superimposed steroid myopathy in a patient with DM/PM who initially improves with glucocorticoids but then develops progressive weakness despite improvement in CPK levels. Treatment is to taper glucocorticoids gradually to avoid a flare in the disease.
- Prophylaxis against *Pneumocystis* pneumonia (PCP) may be desirable, using once-daily single-strength trimethoprim/sulfamethoxazole.

INCLUSION BODY MYOSITIS

Inclusion body myositis (IBM) is the most common inflammatory myopathy in persons > 50 years of age, and it occurs more commonly in men.

IBM is characterized by prominent distal weakness (buzz phrase = "weak handshake"), although proximal weakness can also occur. Dysphagia is often a prominent symptom and can lead to aspiration pneumonia.

History should focus on possible drug exposures (e.g., antimalarials, glucocorticoids, colchicine, statins, cocaine) and alcohol use.

No lab studies are helpful except for muscle biopsy! CPK may be only mildly elevated. Markers of inflammation are absent, and no autoantibodies are developed.

Diagnosis is made by a suggestive history in combination with a muscle biopsy showing vacuoles and filamentous inclusions. Inclusion body myositis is a more indolent disorder and more often affects older males.

Take patients off the precipitating drugs and give high-dose glucocorticoids, but contrary to PM/DM, this myositis is only minimally responsive to treatment.

COLCHICINE MYOPATHY / NEUROPATHY

Colchicine myopathy/neuropathy mimics polymyositis with proximal muscle weakness, paraesthesias, and elevated CPK. Suspect this in the gout patient with renal insufficiency who is taking long-term colchicine. But remember, PM and DM cause myopathy, not neuropathy.

DRUG-INDUCED MYOPATHY

Lipid-lowering drugs and chronic corticosteroids are the most common drugs that cause myopathy.

The common lipid drugs associated with myopathy are statins, fibrates, and ezetimibe, with combinations of the drugs more likely to cause muscle breakdown. Patients present with muscle pain; so, don't disregard the diagnosis if the pain is exercise-induced. Depending

QuickQuiz

- Which autoantibodies are associated with poly- and dermatomyositis?
- Which lipid-lowering drugs cause myopathy?
- Which drugs are used to treat fibromyalgia?

on severity, patients may have weakness of the proximal muscles as well. If the myopathy is severe (weakness, CPK elevations > 3x normal, or myoglobinuria), stop the drugs. Usually, the patients improve when the drug is stopped.

Glucocorticoid myopathy presents traditionally with muscle pain and weakness but is not associated with CPK elevation or an abnormal EMG. It usually occurs in patients receiving high-dose IV corticosteroids or chronic use of prednisone, ≥ 30 mg/day. Consider this as a possible cause of diaphragm weakness in patients who are difficult to wean from the ventilator. Glucocorticoid myopathy is an exclusionary diagnosis; patients will improve when you stop the drugs and start physical rehab.

NONARTICULAR RHEUMATISM

FIBROMYALGIA

Fibromyalgia (FM) is a noninflammatory disorder most likely related to neurotransmitter dysfunction. It seems to be a "neurosensory" disorder characterized by abnormalities in pain processing by the central nervous system. Female: male = 10:1. Patients complain of diffuse muscle aches and stiffness (all day long, usually) and excessive fatigue with a nonrestorative sleep.

The previous American College of Rheumatology (ACR) criteria relied heavily on finding "tender" points on exam.

In 2011, the ACR released new criteria based on a quantitative measure of widespread pain using (in lieu of a tender point exam):

- the widespread pain index (WPI: 0–19), and
- a symptom severity (SS) scale (0–12), which is composed of 4 variables: degree of fatigue, waking unrefreshed, cognitive impairment, and general somatic symptoms.

Significant impairment, consistent with a diagnosis of FM, is defined as:

- WPI > 7 and SS > 5, or
- WPI 3–6 and SS > 9.

(The WPI and SS can be found on the webpage for the American College of Rheumatology at www.rheumatology.org.)

Symptoms must be present at a similar level for ≥ 3 months, and all other causes of similar symptoms must be excluded first. Understand that other entities (e.g., obstructive sleep apnea) can cause symptomatology that will be indexed on the WPI and SS, so fibromyalgia is a diagnosis of exclusion.

Lab studies that help exclude other disorders include ESR, TSH, CPK, CBC, and liver transaminases. Consider a sleep study to rule out sleep apnea or another cause of excessive daytime somnolence.

Associated disorders include: depression, stress, history of emotional trauma, migraines, symptoms of carpal tunnel syndrome (unsupported by EMG), and self-reported yet undetectable Raynaud phenomenon. "Symptomatic" mitral valve prolapse, irritable bowel syndrome, and "chronic fatigue syndrome" diagnoses tend to be in the history of these patients. Fibromyalgia can coexist with autoimmune disorders such as SLE and RA.

Nonpharmacologic therapy is the foundation of FM treatment. Physicians need to set realistic expectations with patients and reassure them that this is not a dangerous condition, while at the same time acknowledging that their pain/symptoms are real. Stress reduction, cognitive behavior therapy, and FM support groups help reduce symptoms. Exercise and sleep restoration are essential components of treatment.

Pharmacologic therapy includes: antidepressants or combinations of antidepressants (low-dose tricyclics +/– SSRIs or reuptake inhibitors), antiepileptics, and/or nonnarcotic analgesics (tramadol).

Tricyclics increase the duration of stage 4 sleep, which has been found to be decreased in these patients. Cyclobenzaprine has a chemical structure similar to TCAs and is also commonly used. In studies, deprivation of stage 4 sleep causes many otherwise healthy people to get the symptoms of fibromyalgia! Whether there is a causal connection is uncertain. Duloxetine and milnacipran are FDA-approved "dual reuptake inhibitors" that block reuptake of both serotonin and norepinephrine. Adding an SSRI or a reuptake inhibitor to a tricyclic is sometimes used in patients who complain of fatigue or exhaustion coupled with mood disturbances.

Pregabalin (antiepileptic) is the first FDA-approved medication specifically for fibromyalgia, but gabapentin is sometimes also used off-label. Both help to alleviate pain. As such, other nonnarcotic analgesic combinations are somewhat effective (acetaminophen + tramadol).

There is an increased incidence of suicidal thoughts in patients taking pregabalin, duloxetine, or milnacipran.

MYOFASCIAL PAIN SYNDROME

Myofascial pain syndrome manifests as myalgias and trigger points. This is different from fibromyalgia in that the pain problem is localized (as in chronic neck pain after whiplash). The trigger points also produce pain in a nearby muscle that is somewhat distal to the trigger itself. This syndrome may be associated with trauma.

Injection of local anesthetic into the trigger points may be helpful. Physical therapy and exercise, muscle relaxers, and sleep improvement are all important components of treatment, as is true for FM.

COMPLEX REGIONAL PAIN SYNDROME

Complex regional pain syndrome (CRPS) is a form of chronic pain that usually affects an extremity. It is divided into 2 types, both with similar signs and symptoms:

- CRPS 1: Previously called reflex sympathetic dystrophy; This type accounts for 90% of the cases and occurs after an illness or trauma in which the nerves in the affected extremity were not directly damaged.
- CRPS 2: Ensues after a direct injury to the nerve.

Generally, the patient has severe pain, tenderness, touch sensitivity, and later also develops tight, cool, shiny skin. Eventually, flexion contractures and x-ray changes of profound osteopenia may develop. Three-phase bone scans may be helpful in diagnosing CRPS (sensitivity is only 40–60%) and in ruling out other causes of bony pain. The most sensitive findings on bone scan include diffuse increased activity with juxta-articular uptake on the delayed (phase 3) images. MRI is very useful in identifying abnormalities in all disease stages.

Treatment consists of NSAIDs; pain modifiers, such as tricyclic antidepressants or gabapentin; physical therapy; short course of glucocorticoids; and nerve block prn. Early, aggressive therapy can prevent the chronic changes described above.

OTHER CAUSES OF NONARTICULAR RHEUMATISM

Other causes of myalgia: Alcohol is the most common myotoxin and can cause acute rhabdomyolysis with very elevated CPK-MM. Hypothyroidism frequently presents with myalgias and stiffness and commonly has an elevated CPK-MM. Polymyalgia rheumatica is discussed under Vasculitis (next).

VASCULITIS

OVERVIEW

Vasculitis is the inflammation of blood vessel walls that can lead to narrowing, obstruction with subsequent ischemia, or aneurysm formation. The clinical presentation is protean and varies according to the histologic type of inflammation, the size of the blood vessels involved, and the organs affected by ischemia. It is typically classified by blood vessel size.

Vasculitis is most often the result of an immune reaction caused by either immune complex deposition or complement activation. It can affect small, medium, or large vessels. Often, vasculitis is hard to diagnose because symptoms may be systemic and nonspecific.

Frequently, presenting signs/symptoms include myalgias/arthralgias, neuropathy, fever, malaise, and weight loss. Anytime you feel palpable purpura or see mononeuritis multiplex in a non-diabetic patient, think vasculitis!

Because of the wide spectrum of symptoms, suspect vasculitis in fever of unknown origin (FUO), especially in those with constitutional symptoms. Also suspect vasculitis when there is no satisfactory explanation for the following conditions: myositis, arthritis, rash, mononeuritis multiplex, multisystem disease, glomerulonephritis, GI, cardiac, or CNS disease.

Again, constitutional symptoms are big in vasculitis. ("Rheumatoid arthritis eats at the joints and nips at the body; vasculitis nips at the joints and eats at the body.")

Typical lab findings include an increased ESR/CRP, thrombocytosis (remember, platelet count is the "poor man's sedimentation rate"), anemia of inflammation, and decreased albumin.

Diagnose with biopsies or angiograms. Skin biopsies may not be specific enough, although polyarteritis nodosa can be diagnosed by skin biopsy in some cases. Muscle and nerve biopsies are very specific, but not very sensitive—although sensitivity increases with an increase in symptoms and with electromyogram (EMG) findings. Do a testicular biopsy if the patient has testicular pain and/or swelling—sensitivity and specificity are good. Kidney biopsies (in a patient with systemic vasculitis symptoms) showing a necrotizing glomerulonephritis with crescent formation is virtually diagnostic for vasculitis (but may be seen in several different vasculitic syndromes). Remember: Biopsy the most involved tissue, when possible.

Quick Quiz

- What are the typical lab findings in a patient with vasculitis?
- What is a typical presentation of GCA? What are the atypical presentations?

LARGE ARTERY VASCULITIS

Overview

Large artery vasculitis includes:

1) Giant cell arteritis +/– polymyalgia rheumatica
2) Takayasu arteritis
3) Aortitis

Giant Cell (Temporal) Arteritis

Giant cell arteritis (GCA), also called temporal arteritis, is part of a spectrum of systemic inflammatory diseases associated with polymyalgia rheumatica (PMR; discussed next).

GCA affects arteries of the head and neck in patients > 50 years of age (average age = 70 years). Female:male ratio is 3:1 (Image 6-19).

Multinucleated giant cells infiltrate blood vessels arising from the aortic arch in a patchy or segmental fashion. Symptoms include temporal headache, diplopia, amaurosis fugax, scalp tenderness, and jaw claudication. Untreated, 40–50% get ischemic optic neuropathy with unilateral irreversible blindness (increased risk in the setting of thrombocytosis; the risk may decrease by adding ASA).

GCA occasionally has a masked presentation; consider it in workups for FUO, failure to thrive, and/or anemia of inflammation.

It also can present similarly to Takayasu's, with symptoms of large-vessel and more peripheral claudication. Extracranial involvement in patients with GCA increases their risk of thoracic aortitis.

Sedimentation rate is virtually always > 60 mm/hr in temporal arteritis; and in patients whose sed rate is not elevated, C-reactive protein (CRP) may be elevated. While extremely rare, GCA can occur even in the setting of a normal ESR and CRP.

Confirm diagnosis by a temporal artery biopsy. Glucocorticoid therapy is started as soon as the diagnosis is suspected. Don't wait for the biopsy! If you suspect GCA you treat right away to decrease the risk of vision loss. While the biopsy should be performed as early as possible, studies show that even a delay of 1–2 weeks doesn't significantly impact biopsy results. Biopsy a large piece of artery (3–5 cm) and do multiple cross-sectional cuts. Even so, because of the patchy involvement, a negative biopsy does not exclude GCA. Bilateral temporal artery biopsies may improve sensitivity but are somewhat controversial.

Image 6-19: Inflamed temporal artery

If a patient with suspected GCA develops vision loss—a medical emergency—treat the patient with high-dose IV glucocorticoids. Otherwise, initial treatment for GCA is prednisone at ~ 60 mg/day. Once symptoms resolve, slowly taper to 20 mg over 1 month, then more slowly over the next 9–12 months. Follow the sedimentation rate because it frequently correlates with disease activity. Low-dose aspirin decreases the risk of stroke during treatment of this disease. Recurrences are especially common during the first year. Steroid-sparing agents may be needed—their use, however, is very controversial at this time.

GCA is a likely Board topic. You may be given an elderly patient with shoulder aches, headache, and vision complaints. You must determine whether the patient has polymyalgia rheumatica (PMR) with GCA, retinal artery occlusion, carotid artery disease, or some ophthalmic disorder. Body pain + vision complaints in the elderly + high sed rate = PMR with GCA! Also know that GCA can present as an FUO or weight loss in the elderly.

Polymyalgia Rheumatica (PMR)

PMR is a clinical syndrome that is classically associated with giant cell arteritis and may be a milder manifestation of the same disease. 20% of PMR patients develop GCA. Conversely, in those with GCA, 50% also have symptoms of or have already been diagnosed with PMR.

A PMR-like illness may be present in other conditions. Elderly onset RA may present as a syndrome indistinguishable from PMR initially, although a significant inflammatory polyarthritis will eventually develop (RF is often negative). Presence of an otherwise unexplained fever in a patient with PMR may indicate the development of GCA.

Think of PMR in the older patient with a history of profound morning stiffness, bilateral shoulder girdle and hip aching, and hand swelling (mimicking RA).

Remember: PMR presents with aching and stiffness, not weakness—in contrast to myositis, which generally presents with weakness, not pain!

PMR can be distinguished from polymyositis by the absence of both objective weakness and elevated muscle enzymes. CK is normal in PMR even though the muscle aches and the patient feels stiff.

Sedimentation rate is usually elevated (> 50 mm/hr) but may be normal in ~ 5%.

Treatment: PMR responds dramatically to low-dose prednisone (about 10–20 mg/day), although it must be slowly tapered, usually over 1–2 years for cure. If the Board exam gives you an older patient with shoulder pain who improves dramatically overnight after 1–2 doses of prednisone, the diagnosis is PMR. PMR may occasionally respond to NSAIDs, which often are preferred in order to prevent the long-term side effects of chronic glucocorticoids.

In atypical cases of PMR, especially those individuals who do not respond to low-dose glucocorticoids (10–20 mg/day with dramatic response expected within 1–3 days), think GCA or an alternative diagnosis, such as cancer.

As with GCA, the ESR correlates with disease activity; so, follow during treatment. If there are any signs of temporal arteritis (e.g., visual changes, headache), you must do a complete reevaluation immediately, including temporal artery biopsy and an increase in the prednisone dose.

Takayasu Arteritis

Takayasu arteritis ("pulseless disease") commonly involves the aorta and its branches. It affects young women (< 40), particularly of Asian descent. This may present initially as an FUO (inflammatory phase); then months to years later, it shows up with claudication or renovascular hypertension with bruits ("pulseless phase"). Patients also may have Raynaud's and erythema nodosum.

Diagnose using conventional angiogram or MR angiogram (MRA) demonstrating large vessel narrowing and/or characteristic aneurysms. Exacerbations or recurrences of inflammation are indicated by an increase in the ESR/CRP, anemia, and artery wall inflammation visible on MRA. Unlike GCA and many of the other vasculitides, tissue biopsy has little role in the diagnosis of this disorder.

Treat with glucocorticoids +/– calcium channel blockers (for hypertension and to prevent any vasospasm) if inflamed. May need anticoagulation for very stenotic vessels. DMARDs and, if needed, TNF inhibitors may be tried as steroid-sparing agents. Cyclophosphamide has been used in severe refractory cases. Takayasu arteritis tends to recur and has a guarded prognosis.

Cardiovascular disease is the major cause of death in Takayasu arteritis. Strict management of traditional cardiovascular risk factors is mandatory.

Aortitis

Aortitis is associated with several systemic inflammatory diseases. Board exams likely will ask about the most common associations: syphilis, endocarditis with mycotic aneurysm, GCA, and spondyloarthropathies. Know that syphilitic aortitis is a tertiary manifestation associated with aneurysm formation and valve regurgitation, but aortic dissection and rupture are extremely rare!

MEDIUM / SMALL ARTERY VASCULITIS

Overview

Most common and frequently tested medium/small artery vasculitides:

1) Polyarteritis nodosa (PAN)
2) Churg-Strauss
3) Granulomatosis with polyangiitis (GPA, previously "Wegener granulomatosis")
4) Microscopic polyangiitis (MPA)

Review the material on ANCAs on page 6-2.

Polyarteritis Nodosa (PAN)

PAN affects medium-sized arteries and is strongly associated with hepatitis B, hepatitis C, and hairy cell leukemia. The vasculitis results in inflammation in the walls of arteries (but not veins) with subsequent formation of aneurysms. Unlike other vasculitides, the inflammation in PAN is not granulomatous; instead, it is marked by the accumulation of neutrophils and mononuclear cells with fibrinoid necrosis.

Symptoms of PAN include anorexia with weight loss, fevers, malaise, arthralgias, mononeuritis multiplex, CNS symptoms, abdominal symptoms, and lower extremity rashes (palpable purpura, livedo reticularis, nodules, and bullae/vesicles). The abdominal symptoms are related to mesenteric arteritis, causing infarct or perforation. Renal involvement usually presents as hypertension, mild proteinuria, and hematuria without red cell casts. Note: PAN does not cause glomerulonephritis; thus, the absence of casts. Instead, disease affects the walls of the arteries that supply blood to the nephron. Essentially, renal ischemia is the primary pathology, with activation of the renin-angiotensin system and development of hypertension.

PAN can affect virtually all organ systems, including the coronaries. But it does not classically cause disease of pulmonary vessels! Patients may present with pulmonary edema as a consequence of left heart failure, but PAN is not associated with pulmonary hemorrhage or infarction. These tidbits help you exclude PAN as a cause of a pulmonary-renal vasculitis.

QuickQuiz

- What are differences in the clinical presentations of myositis and PMR?
- What is a serious complication of PMR? What clinical finding would make you consider that a PMR is developing this complication?
- How does the treatment of PMR differ from the treatment of GCA?
- With which viruses is PAN associated?
- How do you diagnose PAN?
- Which organs/tissues are commonly involved in granulomatosis with polyangiitis (GPA)?
- Which antibodies are specific for granulomatosis with polyangiitis (GPA)?

Suspect a diagnosis of PAN in the patient with multiple diverse symptoms; e.g., chest pain (pericarditis), abdominal pain (mesenteric arteritis), and foot drop (mononeuritis multiplex).

Diagnosis of PAN: If there is no obvious peripheral involvement (e.g., nerve, muscle, testicle), do an angiogram. An angiogram of the mesenteric or renal medium-sized arteries can show diffuse, small, saccular aneurysms or stenoses that are diagnostic. If there is peripheral involvement, biopsy the affected site. Again, biopsy the testicle(s) if pain is present. If the kidney is affected in PAN, the involvement is in the artery (remember: this is not glomerulonephritis), and biopsy is frequently diagnostic. Importantly, ANCA tests are usually negative. These symptoms and a positive ANCA, especially with a positive anti-PR3, are more consistent with a diagnosis of granulomatosis with polyangiitis (previously "Wegener granulomatosis")—definitely not PAN.

Treatment of PAN includes treating chronic HBV, if present, and giving prednisone ± cyclophosphamide, depending on severity at presentation. IV cyclophosphamide-pulse therapy may be less effective at inducing a sustained remission, but it is tried because toxicity is less. PAN is a severe disease, and patients die if not treated (10–20% survive 5 years). Sometimes, treatment only slows the progression of the disease.

There is a skin variant termed "cutaneous PAN" that has skin lesions and neuropathy as clinical features. The skin lesions can be severe and ulcerative, so immunosuppression may still be required.

Churg-Strauss Vasculitis

Churg-Strauss vasculitis is a necrotizing, pulmonary-renal vasculitis marked by eosinophilic granulomas. Patients always have a history of asthma +/– sinus disease or allergies (including allergic rhinitis and nasal polyps).

Lab: peripheral eosinophilia, p-ANCA+, anti-MPO+.

Treatment is the same as for PAN, although many patients respond well to glucocorticoids alone.

Granulomatosis with Polyangiitis

Granulomatosis with polyangiitis (GPA, previously "Wegener granulomatosis") causes necrotizing granulomas, especially affecting the sinuses, lungs, and kidneys (a classic pulmonary-renal syndrome). Patients occasionally develop skin rashes and/or ulcerations and may have migratory large joint arthritis (Image 6-20).

Sinus tissue biopsy in GPA can show any of the following 3 findings:

1) Vasculitis
2) Necrosis
3) Granulomatous changes

The biopsy yield is low because only 30–40% of patients have any 1 of these findings and only 15% have all 3. Even so, any oral, nasal, or sinus abnormality is the preferred first biopsy site because it's the least invasive.

Remember the antibody tests, page 6-2: Patients with GPA are often c-ANCA+ and anti-PR3+, which helps exclude Goodpasture syndrome, which is caused by anti-glomerular basement membrane (GBM) antibodies. Of interest, patients who are anti-GBM+ and c-ANCA+ have a better prognosis than those who are only anti-GBM+.

Courtesy of Seth Remy, MD

Image 6-20: Nodules in Granulomatosis with polyangiitis (GPA)

c-ANCA+ is seen in > 90% of patients with diffuse GPA, but in only ~ 50% with limited GPA. (Limited = usually no renal involvement.) ANCAs occasionally appear in rapidly progressive glomerulonephritis (which can be considered renal involvement of the vasculitis) and in microscopic polyangiitis (MPA, discussed next), but these vasculitic illnesses are usually p-ANCA+ and MPO+.

Diagnosis of GPA is made with biopsy. If the patient has no upper respiratory abnormalities appropriate for biopsy, then biopsy either the kidney or the lung, depending on which is most affected and which biopsy the patient can best tolerate. Renal biopsies are not specific enough to allow differentiation between GPA and microscopic polyangiitis, but the differentiation is not important because the treatment is identical. The point is to get tissue that has an artery in it for diagnosis of vasculitis.

GPA, like PAN, rapidly progresses to death unless treated. The treatment, similar to PAN, consists of cyclophosphamide and high-dose corticosteroids for severe disease. In April 2011, the FDA approved rituximab for remission induction of severe GPA and MPA. In patients with mild pulmonary and renal involvement, methotrexate and prednisone are used instead of cyclophosphamide (defined as normal oxygenation and < 50% increase in creatinine).

Trimethoprim/sulfamethoxazole is prescribed because of increased risk for *Pneumocystis* pneumonia. It is unknown whether it is the illness itself or the cyclophosphamide treatment that predisposes, but preventing this lung infection may help prevent GPA-associated lung exacerbations.

Remember: Side effects of cyclophosphamide include short-term problems, such as bone marrow suppression and infection, and longer-term problems, such as sterility, amenorrhea (higher risk > age 35), bladder effects (hemorrhagic cystitis and cancer), and leukemia/lymphoma.

Microscopic Polyangiitis

Microscopic polyangiitis (MPA) is also a pulmonary-renal syndrome. MPA causes a necrotizing, crescentic glomerulonephritis and may present as an FUO. GPA and MPA are referred to as "pauci-immune" vasculitides since immune complex deposition is not detected to any significant degree, unlike in SLE. MPA never has angiographic changes since it involves small vessels. In older literature, PAN encompassed what we now know as MPA—a separate vasculitic disorder.

Diagnosis is based on biopsy of affected tissue. MPA is often p-ANCA+ and MPO+.

Treatment is essentially identical to GPA.

SMALL-VESSEL VASCULITIDES

Overview

The small-vessel vasculitides are called leukocytoclastic (or hypersensitivity) vasculitides. The common manifestations among these: small vessel involvement, skin involvement (when affected small vessels are near the skin), and leukocytoclasis (PMNs permeating through vessel walls with concomitant cellular death and debris). These hypersensitivity vasculitides are the most common types of vasculitis.

The classic skin finding is palpable purpura—occurring as "crops" of purple papules or large petechiae.

Leukocytoclastic vasculitis is most often idiopathic (40–50%), but common known causes include:

- Drug reactions (especially beta-lactams, sulfonamides, phenytoin, and allopurinol)
- Infections (e.g., viral hepatitis, HIV, endocarditis)
- SLE
- RA
- Henoch-Schönlein purpura
- Cryoglobulinemia
- Systemic vasculitides

Leukocytoclastic vasculitis can be immune complex-mediated, as in those caused by infections and by autoimmune diseases (SLE, RA). This vasculitis group also includes Henoch-Schönlein purpura and vasculitis associated with HCV-associated cryoglobulins.

Leukocytoclastic vasculitis due to a drug reaction can occur 1–10 days after drugs are started. Keep in mind the rash may occur after the drug has already been discontinued (as in antibiotics).

Henoch-Schönlein Purpura

Henoch-Schönlein purpura is an IgA-mediated, small-vessel vasculitis that involves the skin from the waist down (crops of papules), kidneys (biopsy findings identical to IgA nephropathy), and GI tract (abdominal pain and bleeding) with repeated attacks. Some cases have fever. It usually occurs in children, but may be more severe in adults. 2/3 are associated with viral URIs and streptococcal infections. It is sometimes associated with elevated IgA levels.

Diagnosis can be confirmed by identifying the presence of IgA deposits in the vessel wall on skin biopsy. It is usually benign and resolves spontaneously but occasionally causes renal failure (up to 10% of adults and < 5% of children). Treatment is often supportive. Glucocorticoids may improve joint and GI symptoms, but there is no compelling evidence that they help the kidney disease. Give corticosteroids or cytotoxic agents only for life-threatening symptoms.

Quick Quiz

- Why is trimethoprim/sulfamethoxazole given to patients with granulomatosis with polyangiitis?
- Leukocytoclastic vasculitis is associated with which diseases?
- Mixed cryoglobulinemia is associated with which hepatitis virus?
- What are the clinical features of Behçet's?

Cryoglobulinemia

Cryoglobulins are immunoglobulins that precipitate in a serum specimen when chilled < 98.6° F and redissolve when warmed. They are normally cleared by the liver. Buildup occurs with overproduction or decreased elimination from chronic liver disease.

There are 3 types of cryoglobulinemia. Type II, caused by chronic hepatitis C (HCV) infection, is by far the most common. Because Types II and III have immune complexes consisting of IgM and IgG, they are called "mixed" cryoglobulinemias. The IgM in these 2 types is a rheumatoid factor (antibody against the Fc portion of IgG), which activates the complement cascade. Let's go over the characteristics of each type.

Type I is the least common (10–15%). It is due to a single monoclonal antibody (IgM, IgG, or IgA) and is usually found in patients with multiple myeloma or Waldenström macroglobulinemia.

Type I does not have rheumatoid factor activity like Types II and III; hence, complement is not activated. Therefore, patients are usually asymptomatic until the cryoglobulin level rises high enough to cause symptoms of hyperviscosity such as neurologic symptoms (headache, blurred vision, vertigo, deafness, nystagmus), livedo reticularis, purpura, and Raynaud phenomenon.

Type II (essential mixed cryoglobulinemia) is the most common (50–60%). Type II cryoglobulin is an immune complex consisting of monoclonal IgM rheumatoid factor attached to polyclonal IgG. Most patients have an associated hepatitis C (HCV) infection.

Type III (25–30%) is similar to Type II but has immune complexes composed of polyclonal IgM rheumatoid factor and polyclonal IgG. Half of patients have HCV infection and the others usually have a chronic autoimmune disorder (e.g., SLE) or a lymphoproliferative malignancy.

Types II and III cryoglobulinemia produce similar symptoms. They both activate complement and frequently present with vasculitis, most commonly with lower extremity purpura, glomerulonephritis, peripheral neuropathy, and low complement levels. Patients may eventually get hyperviscosity symptoms discussed in Type I.

Patients with HCV and mixed cryoglobulinemia can get membranoproliferative glomerulonephritis (MPGN). These patients have low C3, C4, and CH50 (classical complement activation), and their rheumatoid factor (RF) is very high (because Types II and III are RFs). MPGN frequently causes renal failure. When the patient gets renal disease, prognosis is poor.

Treatment with pegylated interferon alfa and ribavirin (+/– new protease inhibitors) is often effective for the vasculitis caused by HCV. In patients with more severe disease (visceral or renal), glucocorticoids or more potent agents may be required.

DDx: Do blood cultures to exclude endocarditis. Other diseases that mimic this form of vasculitis include cardiac myxoma emboli and cholesterol atheroembolism. Obtain an echocardiogram when emboli are suspected. Especially consider cholesterol atheroembolism in a patient with severe atherosclerosis who has just had an arteriogram. This is important if the patient has hypereosinophilia (90% of patients) and/or hypocomplementemia (50% of patients). Skin biopsy confirms the diagnosis of cholesterol atheroembolism.

Relapsing Polychondritis

Relapsing polychondritis is inflammation of cartilage in the ear, nose, larynx, and trachea. It also can cause arthritis, ocular disease (scleritis, iritis), hearing loss/vertigo, and vasculitis. It can cause aortic dilatation and a valvulitis leading to aortic and/or mitral regurgitation. Suspect in a patient presenting with hoarseness, saddle-shaped deformity of the nose, and swelling of the ear's cartilage! The ear lobe is spared (no cartilage). Glucocorticoids are the cornerstone of treatment and occasionally steroid sparing agents are required.

BEHÇET DISEASE

Behçet disease is a vasculitic syndrome that occurs mainly in people of Middle Eastern, Japanese, or Asian descent. It is a multisystem disease: painful, recurrent aphthous stomatitis; genital aphthous ulcers; synovitis; variable cutaneous lesions (erythema nodosum, vasculitis, acneiform, pathergy, dermatographism); and CNS disease (recurrent aseptic meningitis). It may also cause aortic, coronary, or pulmonary artery aneurysms. Aneurysmal rupture carries a high mortality rate. Most have inflammatory eye disease (e.g., uveitis, optic neuritis, retinal vasculitis), which is a common cause of blindness. Skin is hyper-reactive to minor trauma such as

needle sticks (pathergy)—resulting in a papule or sterile pustule 1–2 days later. The pathergy test is fairly specific for Behçet's but not very sensitive. Cause is unknown.

First-line therapy for oral and genital ulcers includes topical glucocorticoids or sucralfate. First-line oral therapy should be colchicine. Treat more severe disease (vascular or neurologic) with systemic corticosteroids, azathioprine, cyclophosphamide, and anti-TNF biologic agents. Relapse is common.

ANTI-GLOMERULAR BASEMENT MEMBRANE SYNDROME

Anti-glomerular basement membrane (GBM) syndrome is a disease that results from anti-GBM antibodies that deposit in the lungs and kidneys. The clinical presentations include a rapidly progressive glomerulonephritis (termed "anti-GMB disease"; patients usually > 50 years old and more often female) or a rapidly progressive glomerulonephritis with pulmonary hemorrhage (termed "Goodpasture syndrome"; patients usually < 30 years old and more often male). This syndrome is not a vasculitis, and most patients do not have any constitutional signs of disease.

Goodpasture's has a bimodal age distribution: 20–30 years (M > F) and 60–70 years (F > M). Smoking has a strong correlation with alveolar hemorrhage, especially in young males.

Diagnose anti-GBM disease by measuring anti-GBM antibodies in the serum and with renal and/or lung biopsy, which will demonstrate evidence of the anti-GBM antibodies on immunofluorescence.

~ 40% of patients who are anti-GBM+ also will be ANCA+ and may have symptoms of systemic vasculitis. These patients with double antibodies are treated the same as patients with anti-GBM only.

Note that patients with pulmonary hemorrhage may have an increased DLCO.

Treatment involves plasmapheresis to remove circulating anti-GBM antibodies and immunosuppression with glucocorticoids and cyclophosphamide to inhibit further autoantibody formation.

Remember the rheumatic diseases that can cause pulmonary hemorrhage and pulmonary-renal syndromes:

- Goodpasture syndrome
- SLE
- GPA
- MPA

RHEUMATOLOGY POINTS WITH MALIGNANCY, DIABETES, & PAGET'S

Malignancy (covered in Oncology section, Book 4):

- Hypertrophic pulmonary osteoarthropathy (HPOA) (page 6-24)
- Amyloidosis (Check with rectal biopsy or an abdominal fat pad biopsy.)
- Secondary gout
- Carcinomatous polyarthritis (Resembles RA; especially consider with breast cancer or leukemia.)

Diabetes (more in Endocrinology section, Book 4):

- Dupuytren/flexion contractures occur in Type 1 diabetes. This and the preceding limited joint mobility are known as cheiroarthropathy. This may also present with thickening of the skin of the fingers. (Remember that systemic sclerosis causes thickening of skin proximal to the metacarpals in addition to the fingers.) On physical exam, the "prayer sign" may be seen. This is the patients' inability to press their palms together completely without a gap remaining between opposed palms and fingers.
- Carpal tunnel syndrome
- Frozen shoulder
- Foot disorders that include neuropathic arthropathy (page 6-24)
- Osteomyelitis

Paget disease of the bone (covered in Geriatrics in General Internal Medicine section, Book 5):

- Osteoarthritis.
- Fractures, including stress fractures.
- Serum alkaline phosphatase and urinary hydroxyproline are elevated because both of these are indications of increased bone turnover.
- Osteosarcoma occurs in about 1%!

First-line treatment for Paget disease is bisphosphonates. Teriparatide should not be prescribed for these patients because it is associated with osteosarcoma and patients with Paget's are already at increased baseline for this condition.

OFFICE ORTHOPEDICS

OVERVIEW

Know this section very well. The common aspects of office orthopedics and rheumatology will very likely be on the Boards.

Quick Quiz

- Name some bursae that commonly become inflamed.
- What is the workup for nontraumatic synovitis?

OSTEOPOROSIS

Osteoporosis is covered in the General Internal Medicine section, Book 5, under Geriatrics.

BURSITIS

Bursas are small fluid-filled sacs that function to provide a gliding surface to reduce friction when muscles and tendons, slide across bone. Healthy bursas are necessary for a smooth, frictionless surface making normal movement painless. Bursitis is the inflammation of a bursa secondary to mechanical irritation, bacterial infection, RA, or gout (last two especially common in the olecranon bursa). Bursitis or tendinitis usually causes severe pain with any active movement of the joint—especially against resistance. Passive range of motion is much less painful or even painless.

Prepatellar bursitis (housemaid's knee), olecranon bursitis (student's elbow), trochanteric bursitis, subacromial bursitis, and pes anserine bursitis are the most frequently tested—probably because they are the most common. Know that the knee has several bursas (suprapatellar, infrapatellar, prepatellar, and pes anserine), and that the pes anserine bursa is located on the medial aspect, just inferior to the knee. Pes anserine bursitis is described as pain +/– swelling ~ 2 cm inferior and medial to the patella. In all locations, there is frequently a serosanguineous effusion within the bursal sac. More information on these bursitis presentations is included later in this section.

Diagnosis is usually clinical but requires exclusion of infectious bursitis if the area is inflamed and/or the patient is systemically ill, especially in patients on immunosuppressants; e.g., patients with RA on chronic corticosteroids. Aspiration of the bursa with fluid studies, including Gram stain and culture, helps you determine whether infection is present. If no sample is obtained for microbiology, treat empirically with an anti-staphylococcal drug.

Treatment consists of rest of the affected area. Glucocorticoids can be injected, provided that the bursa is not infected. Mild infection in immunocompetent patients can often be treated with oral antibiotics, but serious infections in immunocompromised patients should be treated parenterally. Resistant, chronic cases sometimes require surgical excision of the bursa.

JOINT PAIN

Overview

When an extremity joint is acutely swollen without a history of trauma, it should be tapped and analyzed for crystals, cell count with differential, and Gram stain with culture.

A word about terminology: "Abduction" = away from the midline; "adduction" = toward the midline. "Dorsiflexion" = pulling the foot upwards, as in taking the foot off the gas pedal. "Plantarflexion" = pressing the foot down, as in pressing on the gas pedal.

Shoulder

True shoulder pain usually extends from the acromion to the insertion of the deltoid. Refer to Figure 6-2 through Figure 6-4 as you read this topic.

Thoracic Outlet Syndrome

Problems in the neck/shoulder can cause irritation of the brachial plexus as it moves from the neck and chest cavity into the arm. Impingement of the nerves causes shoulder pain that may be localized or extend from the base of the neck, over the top of the shoulder, and down the arm. This pain may extend into the hand and is often accompanied by paresthesias and weakness. If the vascular supply is also affected, patients will have hand claudication +/– Raynaud's and ulcers in severe cases.

Diagnosis is difficult because PE is usually normal unless certain maneuvers (e.g., Adson maneuver) are used to elicit abnormalities in the pulse or paresthesias and weakness. If you suspect the syndrome, do a chest radiograph (looking for cervical ribs that sometimes are a cause) and/or EMGs with nerve conduction studies to see if the brachial plexus is affected.

Treat with shoulder exercises and education about avoiding the postures that elicit symptoms. Cervical ribs can be surgically removed if they are the cause.

Shoulder OA

Repetitive use of the joint and trauma can cause osteoarthritis, which is more common in the acromioclavicular joint than in the glenohumeral joint. Pain can be anterior in the shoulder or nebulous and ill-defined. Although x-ray films can appear normal early on, they may show joint-space narrowing and osteophytes over time. Treat as you would all cases of OA with education and nonnarcotic analgesics. Surgery is used only in very refractory cases.

Amyloidosis

Long-term dialysis patients are likely to get amyloid deposition (beta-2 microglobulin) in the joints. This

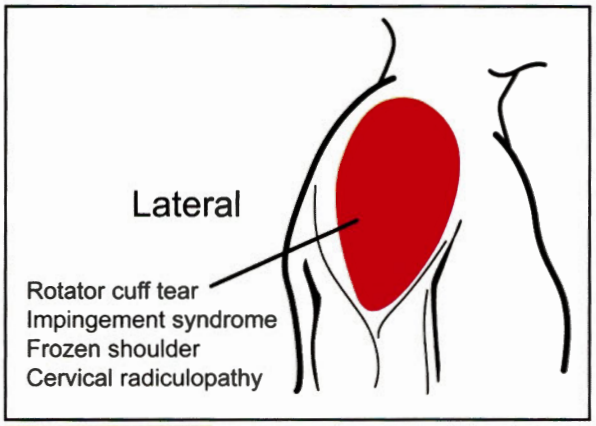


Figure 6-2: Shoulder Lateral View

causes painful joints and tends to affect the shoulder and wrist, causing carpal tunnel syndrome.

Adhesive Capsulitis or "Frozen Shoulder"

This is most commonly seen in patients who are 40–60 years of age and who have underlying predispositions; e.g., another painful shoulder condition causing disuse, such as bursitis, fracture, or rotator cuff injury; diabetes is also a risk factor. However, the shoulder can develop adhesive capsulitis with no apparent cause.

Diagnosis is suggested by shoulder pain, stiffness, and decreased range of glenohumeral motion in all directions. PE shows significantly reduced range of motion (< 50% of normal), both actively and passively, in all directions. Radiographs are normal.

Symptoms typically resolve in 6–12 months, and range of motion is regained if the patient performs shoulder exercises. Intraarticular corticosteroids are occasionally used. Refractory cases may require surgery (< 10% of cases).

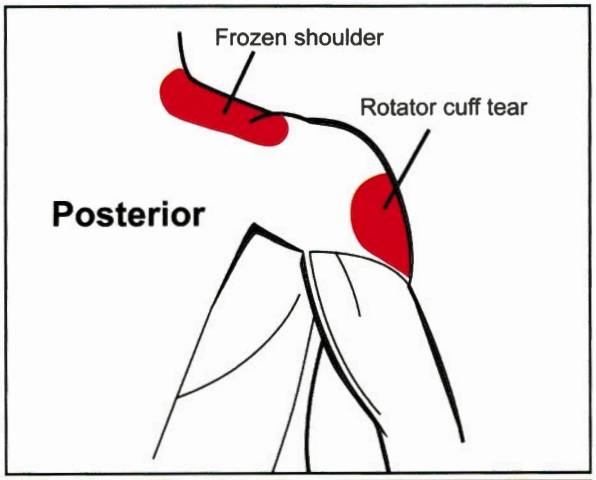


Figure 6-3: Shoulder Posterior View

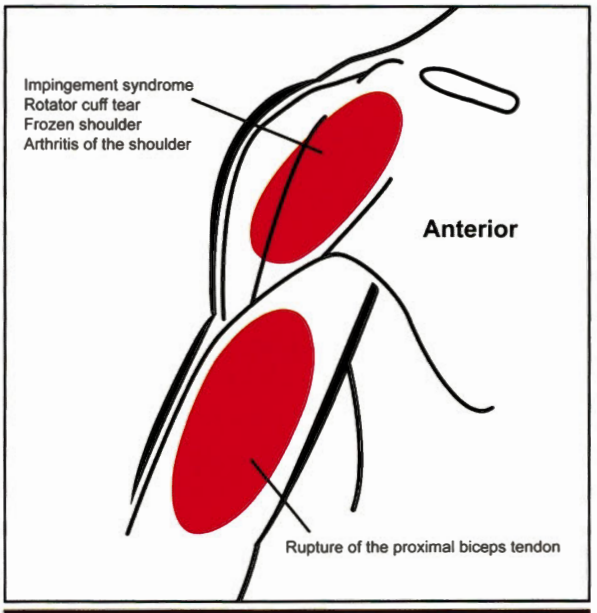


Figure 6-4: Shoulder Anterior View

Impingement Syndrome

This syndrome refers to compression of the subacromial bursa or regional tendons in the space between the acromion and the humeral head. The biceps tendon and all of the rotator cuff tendons go through this area. For this reason, biceps tendonitis and some rotator cuff injuries are often considered impingement syndromes.

Impingement presents with pain when reaching overhead or at night, especially while lying on the affected shoulder. Except in longstanding cases, strength in the shoulder is normal.

Certain provocative maneuvers can elicit the pain. If any of the following tests elicit pain, the patient likely has an impingement syndrome:

- **Neer** test: Patient attempts to shrug his shoulder as you apply downward pressure to prevent the shrug, while passively lifting the arm toward the ear (forward flexion of glenohumeral joint).
- **Hawkins** test: Flex the patient's elbow and internally rotate the shoulder.
- **Yocum** test: While the patient touches the uninvolved shoulder, lift up on the flexed elbow.

Diagnosis of impingement is clinical; imaging is usually performed only when patients are refractory to therapy and require orthopedic referral.

If strength is normal, conservative management is best initially: rest from aggravating activities, ice, and physical therapy for 3 months. Treat the pain with a short course of NSAIDs. Intraarticular glucocorticoid injections sometimes are used if the patient doesn't get better quickly.

QuickQuiz

- Name and characterize 3 tests to assess shoulder impingement.
- Compare and contrast the presentation of shoulder OA, subacromial bursitis, impingement, and rotator cuff injuries.
- Olecranon bursitis is associated with what systemic diseases?
- How is lateral epicondylitis treated?

Refer for ortho evaluation if the patient still has pain after 3 months of therapy or if weakness is present at initial evaluation, which might suggest a rotator cuff tear.

Subacromial Bursitis

This is also called deltoid bursitis. Patients present with pain both at rest and with movement. The pain with this bursitis is referred to the lateral aspect of the arm. Consider this diagnosis when the patient reports waking from sleep with pain in the shoulder and arm. It can be associated with a rotator cuff tear (definitely consider if weakness is present) and causes of impingement.

On exam, the middle arc of the active abduction is painful, while the extremes are painless. Several other problems can cause this "painful arc" syndrome; e.g., calcification/tear/tendonitis of the supraspinatus tendon or a crack in the humeral tuberosity, where the supraspinatus tendon attaches. Occasionally, pain is so severe that the patient cannot accomplish any active movement, especially abduction. Passive range of motion shows pain with abduction but usually is otherwise painless.

Treat with rest and nonnarcotic analgesics. Intrabursal glucocorticoid injections can also be used if the patient does not respond to more conservative measures.

Rotator Cuff Abnormalities

Injuries or degeneration of the rotator cuff are the most common causes of shoulder pain. Some tears, even severe ones, can sometimes occur without pain—and manifest only as weakness! Consider a tear in patients who play overhead sports (e.g., baseball), have had shoulder trauma, are older than 50 years, or have RA.

Pain with overhead reaches and night pain are classic features. The injury can also cause a subacromial bursitis, so always suspect a tear when patients present with bursitis features.

Exam in partial tears demonstrates the painful arc syndrome +/– weakness. The trick here is to determine whether weakness is due to pain or true muscle tear, since patients with pain will guard their shoulder (lidocaine injections help in this situation). Another exam maneuver is to observe active adduction: Patients who cannot adduct smoothly (called the "drop-arm sign") may have a tear.

Complete rotator cuff tear is very debilitating. It usually involves separation of the supraspinatus tendon, but it may involve the adjacent subscapularis or infraspinatus tendons. These tendons blend with the shoulder joint capsule, and a separation of the tendons usually involves the joint capsule. This allows "communication" between the shoulder joint and the subacromial bursa. Complete tears usually occur in patients > age 60. Patients are unable to abduct the arm due to weakness +/– pain, except by rotation of the scapula (shrugging the shoulder).

If you suspect a tear, start with plain radiographs because they can sometimes show you abnormalities in the positioning of the humeral head, acromion, and glenoid. MRI can also make the diagnosis, but abnormalities have to be clinically correlated because lots of asymptomatic people have tears visible on MRI.

Treatment of most tears is conservative: rest, nonnarcotic analgesics, and physical therapy, except for full-thickness tears in a healthy person → surgery. Also consider surgery when conservative treatment fails.

Elbow

Olecranon Bursitis

This type of bursitis can be traumatic, septic, gouty, or due to RA. Traumatic bursitis ("student's elbow") is caused by chronic pressure. The bursa should be aspirated if there is any question about possible infection.

Treat uninfected bursitis with aspiration and NSAIDs or glucocorticoid injection.

Treat septic bursitis with incision, drainage, and antibiotics. Oral antibiotics can be used for mild infections—IV is needed in severe inflammation. (See Figure 6-5.)

Lateral Epicondylitis

"Tennis elbow" presents with tenderness and pain well localized to the front of the lateral epicondyle of the elbow, where the extensor tendons of the forearm insert. Symptoms usually resolve spontaneously with decreased use of the elbow, although it may take 2 or more years. Treatment: NSAIDs and splinting to reduce supination/pronation motion; consider a glucocorticoid injection.

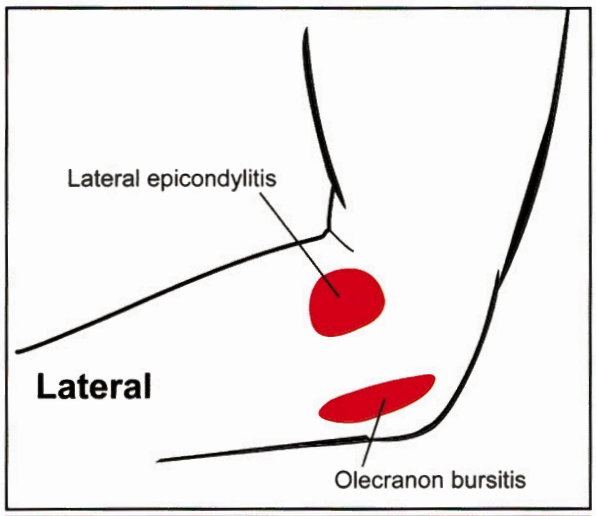


Figure 6-5: Elbow Lateral View

Wrist

Volkmann Contracture

Supracondylar fractures can be associated with a compartment syndrome that develops after damage to the brachial artery. Subsequent ischemia can cause this contracture of the wrist and fingers. Suspect a brachial artery problem in a patient presenting with trauma to the elbow and an unwillingness to extend the fingers due to pain.

Carpal Tunnel Syndrome

Carpal tunnel presents as paresthesias and dysesthesias in the median nerve distribution (thumb through middle finger) that can be reproduced by tapping on the volar aspect of the median nerve (Tinel sign) and/or forced flexion of the wrists for 20–30 seconds (Phalen test).

Certain groups of patients are more susceptible; e.g., pregnant women or those on oral contraceptives; dialysis patients; and any arthropathy associated with wrist synovitis. Both hypothyroidism and acromegaly are also associated.

Pain only in the shoulder or elbow is an atypical presentation. Nerve conduction studies aid in the diagnosis.

Initial treatment consists of a wrist splint worn day and night for 3–4 weeks. Conduct carpal tunnel release in patients with axonal (motor) loss or in cases refractory to conservative treatments, such as splinting or steroid injections.

Ganglion Cyst

Ganglion cysts can occur at any joint or tendon sheath, but they are most commonly found on the dorsum of the wrist at the scapholunate joint. The cyst is attached to a tendon sheath or the joint capsule. There is no communication between the inside of the joint capsule and the interior of the ganglion. They are usually asymptomatic but may cause an ache. Ganglions generally are not treated, but temporary resolution may be provided by firm pressure or aspiration. The old remedy was slamming the ganglion with the family bible! But this should be avoided because it may cause an inflammatory response and may recur. Definitive treatment is surgical.

De Quervain Tenosynovitis

This is a chronic or subacute inflammation of the flexor tendons or the abductor pollicis longus tendon of the thumb. It is characterized by pain and well-localized tenderness over the styloid process of the distal radius. It is often caused by repetitive stress of the wrist with certain motions, like wringing clothes. The Finkelstein test (forced ulnar motion of the wrist with the thumb adducted) reproduces the pain. Natural healing is very slow. Splinting, steroid injections, and NSAIDs can be beneficial for milder cases. Surgery, which is curative, should be reserved for patients with severe disability.

Hand

Dupuytren Contracture

This finger flexion is caused by thickening and contraction of the palmar fascia. The palmar fascia extends from the termination of the palmaris longus tendon on the wrist to the proximal and middle phalanges of the fingers. As the contraction progresses, you can see cord-like bands on the surface of the palm. The cause is unknown, but these contractures are associated with diabetes, alcoholism, malignancies, and recurrent occupational vibratory stimuli. The cornerstone of treatment has been surgical, but contractures tend to recur in the young. In 2010, the FDA approved collagenase clostridium histolyticum for the treatment of Dupuytren contracture with a positive cord. This medication, which contains 2 collagenases, is injected into the "cord" and provides hydrolyzing activity on the collagen, which helps reduce the degree of contraction and improve range of motion.

Paronychia

Suppuration of the finger around the cuticle is a paronychia.

Acute paronychia is caused by thumbsucking; trauma; chronic water immersion; or neglected, manicured ("fake") nails. It presents as an erythematous, painful nail fold.

Over time, if the cause is bacterial, the area can become abscessed—usually by *S. aureus* or oral flora (thumb suckers).

QuickQuiz

- What is the difference between a felon and a paronychia?
- What procedure do you not perform to treat herpetic whitlow?
- How does pain from hip OA differ from pain from trochanteric bursitis?
- Which patients are at risk for avascular necrosis of the hip?
- Should MRI evaluation of avascular necrosis include one or both hips? Why?

Chronic paronychia is seen in immunocompromised patients (e.g., diabetics, HIV/AIDS) and is often due to candidal species. Severe immunosuppression predisposes to pseudomonal paronychia.

Treatment of paronychia is incision and drainage (with cultures if you suspect fungus or *Pseudomonas*), followed by antimicrobials.

Felon

Infection of the pulp space on the palmar side of the distal phalanx is a felon and is a more severe infection than paronychia, requiring surgical intervention to drain collected pus.

Herpetic Whitlow

Be certain to distinguish an abscess from herpetic whitlow, which presents similarly but is treated conservatively. Whitlow is caused by herpetic viral infection of the finger—vesicles presenting anywhere on the fingertips, even on the distal surface.

A good history and PE helps you differentiate herpetic whitlow from bacterial and fungal paronychia or felon. Whitlow is associated with occupational exposure to oral secretions; e.g., dentistry, anesthesiology, or thumbsucking in a child with recent herpetic gingivostomatitis. Also, whitlow initially presents with vesicles on an erythematous base. If you can't distinguish, viral cultures of the lesions are helpful.

Surgery causes herpetic whitlow to worsen, so do not perform incision and drainage on whitlow lesions!

Trigger Finger

When a finger gets "stuck" in flexion at the PIP joint, we call it "trigger finger" or digital tenosynovitis stenosans. It is "unstuck" only with strong effort or with passive movement using the other hand—which causes significant pain. There is tenderness at the base of the finger (palmar aspect). The cause is swelling of the flexor tendon and the opening of the flexor tendon sheath at the base of the finger.

Splinting and local steroid injections can help, but a simple surgery is required to cure the condition. It consists of incising the mouth of the fibrous flexor sheath longitudinally.

Hip

Trochanteric Bursitis

This bursitis is the most common cause of lateral thigh discomfort. Patients report "hip" pain when lying on the involved side, draping the involved leg over the non-involved limb, or bearing weight on the affected side. When asked specifically to point to the area of most intense pain, patients with bursitis will point to the lateral aspect of the thigh over the trochanter (Figure 6-6 and Figure 6-7). This helps to distinguish bursa pain from true hip joint pain, which causes a point of maximum intensity in the groin (may radiate to the buttock).

NSAIDs, local heat, or PT and/or glucocorticoid injections are very helpful.

Avascular Necrosis (AVN)

Patients on chronic glucocorticoids or who abuse alcohol have a significant risk of AVN of the femoral and humeral heads. Other causes include sickle cell disease, pregnancy, HIV/AIDS, Gaucher disease, hypercoagulable states, and pancreatitis. AVN can also occur in lupus patients without prior use of glucocorticoids. It may also be idiopathic or post-traumatic. Patients with femoral neck fractures or traumatic hip dislocations are especially susceptible because the blood supply to the femoral head is disrupted.

AVN is best diagnosed early with an MRI. If diagnosed early (when plain films are still normal), a revascularization procedure may prevent the need for hip replacement. Be certain to image both hips with either plain films and/or MRI because the risk of bilateral AVN is high, even if the patient is not symptomatic in the alternate hip (called "Stage 0").

Hip OA

Hip osteoarthritis presents as increased pain with use that is relieved with rest; the maximum point of pain intensity is localized to the groin (Figure 6-6 and Figure 6-7), a feature that distinguishes hip joint pain from trochanteric bursitis. The pain may also refer to the knee. Patients may complain of morning stiffness (< 30 minutes) and "gelling" (stiffness that occurs after inactivity and resolves with use).

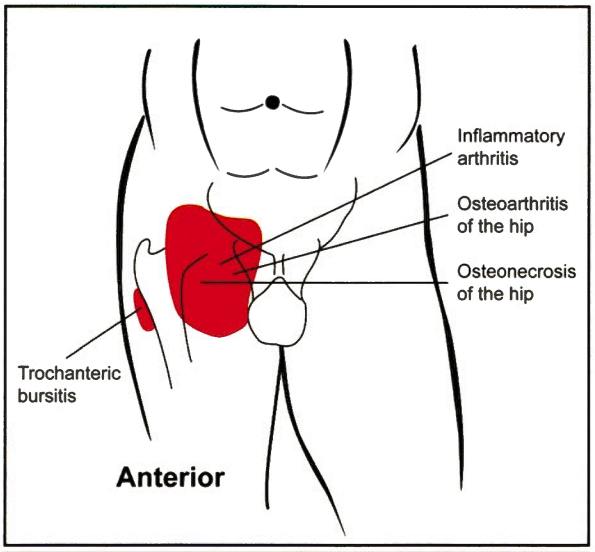


Figure 6-6: Hip Anterior View

Know that obesity does not contribute to the development of hip OA, although many patients with hip OA are obese.

Exam usually does not reveal any inflammation, but decreased range of motion and crepitus might be obvious. Standing or "weight-bearing" radiographs show joint-space narrowing +/– subchondral sclerosis and/or osteophytes. In patients with typical pain and radiographs, no further imaging is necessary.

Treat patients with education on weight loss and nonnarcotic analgesics. Conservative measures should be exhausted (especially weight loss, physical therapy, and use of assist devices, such as canes) before referral for total hip arthroplasty.

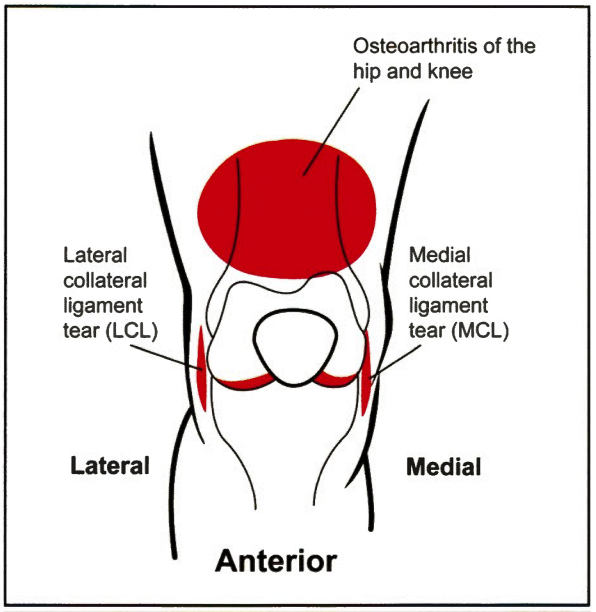


Figure 6-8: Knee Anterior View

Knee

Knee OA is discussed on page 6-15. (See Figure 6-8.)

Baker Cyst (Popliteal Cyst)

This is simply a posterior herniation of the synovial cavity of the knee caused by a tense knee effusion (Figure 6-9). This forms a synovial, fluid-filled sac in the midline behind the knee or in the upper calf. A Baker cyst usually occurs as a result of chronic arthritic conditions in which there is persistent synovial effusion (e.g., rheumatoid arthritis) or meniscal tears. If an arthritic patient with knee involvement presents with a

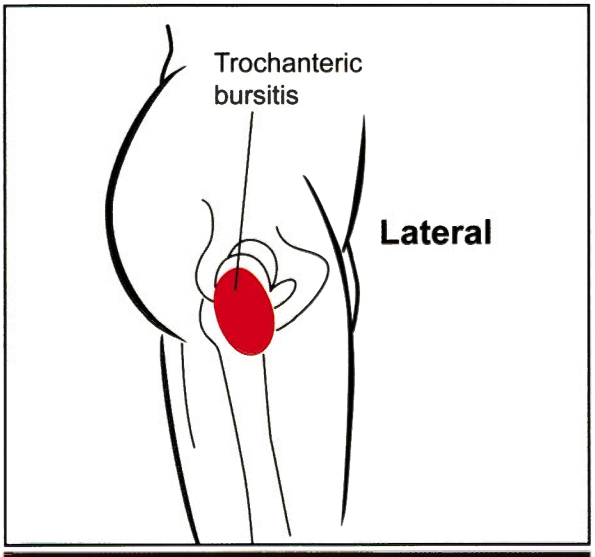


Figure 6-7: Hip Lateral View

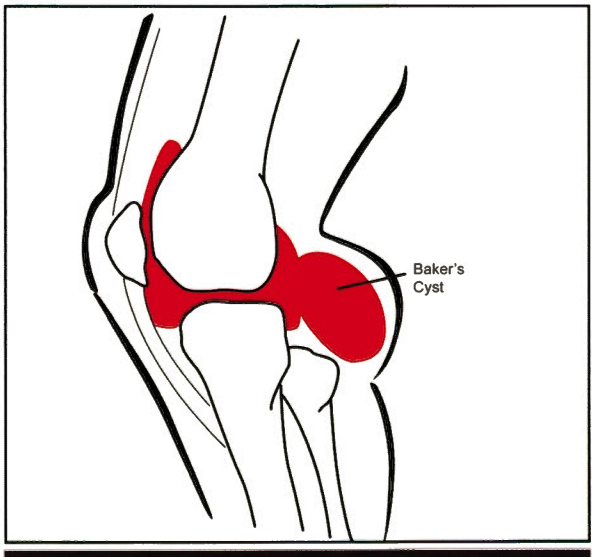


Figure 6-9: Lateral View of Baker Cyst

QuickQuiz

- What intervention can relieve a Baker cyst?
- What is the specific presentation of pes anserine bursitis?

swollen calf, besides phlebitis, suspect a ruptured Baker cyst causing pseudo-phlebitis.

Prognosis is usually good.

On exam, the cyst can be palpated in the posterior knee when the knee is partially flexed. Or, have the patient stand and look at the posterior knee for swelling. Occasionally, a Baker cyst can cause extrinsic venous compression that can also simulate phlebitis. Of course, you should rule out deep venous thrombosis (DVT); and sometimes, an ultrasound can also see the cyst. Know that once DVT is excluded, you do not need to do an MRI to make a diagnosis of Baker cyst—further imaging adds no useful information.

Treatment is rest, NSAIDs, and treatment of the underlying cause. If the cyst is very large or causes significant pain, you can aspirate the knee (not the back of the knee!) and inject glucocorticoids. Refractory effusions may have to be surgically removed.

Prepatellar Bursitis ("Housemaid's Knee")

This bursitis localizes pain over the patellar bursa and is caused by kneeling on hard surfaces (Figure 6-10). If the symptoms get progressively worse with treatment, there may be a bacterial infection of the bursa, which may occur without an obvious source.

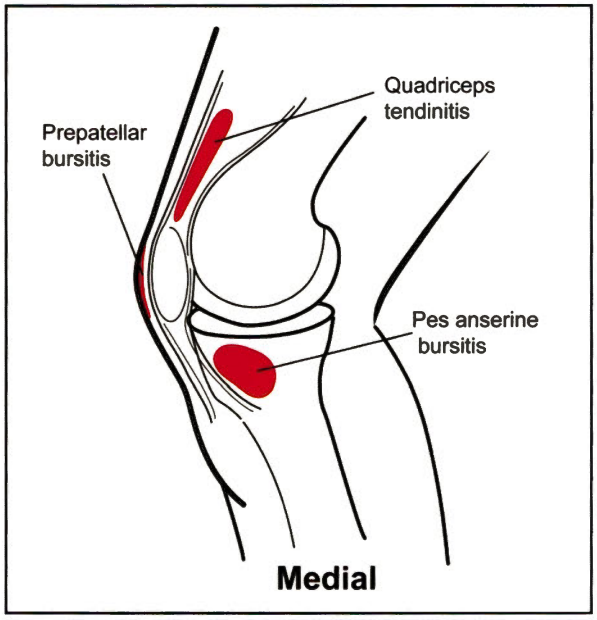


Figure 6-10: Knee Medial View

Remember to aspirate and exclude infection as a cause if there's any question about the source.

Treatment is rest, analgesics, +/– steroid injection.

Pes Anserine Bursitis

This bursitis is caused by inflammation of the pes anserine bursa, located over the medial aspect of the proximal tibia 2 inches below the knee joint line (Figure 6-10). This is just proximal to the area where the 3 tendinous extensions of the gracilis, sartorius, and semi-tendinous muscles insert into the medial aspect of the tibial tuberosity.

Symptoms are pain in this area—especially when climbing stairs.

Remember to aspirate and exclude infection as a cause if there's any question about the source.

Treatment is rest, analgesics, +/– steroid injection. Diabetes may be a predisposing factor.

Pigmented Villonodular Synovitis (PVN)

PVN is an idiopathic, monoarticular, benign synovial tumor that causes recurrent hemarthrosis, usually of the knee in young adults. Patients have recurrent bleeding into the knee, resulting in a darkly pigmented joint aspirate.

MRI is diagnostic.

PVN responds to synovectomy or radiation for recurrent cases.

Spontaneous Osteonecrosis of the Knee (SONK)

SONK can occur as a result of mild trauma in the elderly (60–70-year-olds), especially women. Predisposing factors include recurrent knee glucocorticoid injections, trauma, or systemic disease; e.g., SLE. Weight-bearing pain is present initially on the medial aspect of the knee, and symptoms often resolve spontaneously.

Do an MRI to exclude a tear in a meniscus.

Most are treated conservatively. In contrast to secondary osteonecrosis which requires arthroplasty, nonoperative treatment has been shown to produce good results in symptomatic patients with SONK.

Foot

Morton Plantar Neuroma

This benign neuroma causes painful, burning paresthesias and tenderness in the interdigital webbing due to repeated nerve trauma. Patients may feel like they are standing on a pebble in their shoe. It is usually unilateral and most often appears between the 3rd

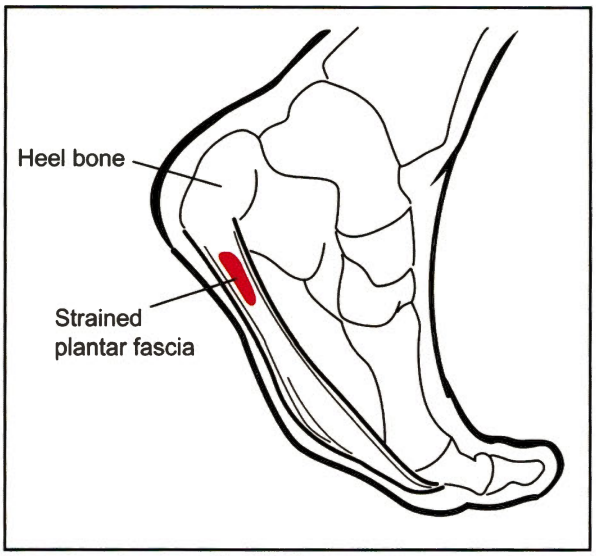


Figure 6-11: Plantar Fasciitis

and 4th toes. Treatment is metatarsal arch support or glucocorticoid injection; however, severe cases may require surgery.

Plantar Fasciitis

This foot pain occurs most commonly in patients 40–60 years old, with increased incidence in runners and ballet/aerobic dancers (Figure 6-11). The cause is not known. The hallmark of plantar fasciitis is a history of severe heel pain with the first couple of steps in the morning or after other long periods without weight-bearing.

Radiographs are usually not necessary, but can assist in excluding diseases that present similarly, such as calcaneal stress fractures and Paget disease. Look for evidence of a spondyloarthropathy in any patient who presents with plantar fasciitis.

Treatment is conservative: rest, NSAIDs, avoidance of heel impact, shoes with arch support, and heel inserts. Injection of mixed steroid/anesthetic can be done in refractory cases. Recurrent steroid injections should be avoided because they cause fat pad atrophy.

Low Back Pain

Overview

Acute lower back pain (LBP) is one of the most common reasons why patients visit their primary care doctor. There are several causes of nonspecific, acute back pain. These include a moderately prolapsed disk, catching of the synovial membrane in a facet joint, transient subluxation with ligament strain, and basic muscle strain. Certainly worse diagnoses can cause lower back pain (e.g., spinal stenosis or metastatic cancer), so your task is to differentiate the simple causes from ones that require imaging and/or aggressive treatment.

Muscle Strain

More than 50% of adults will experience at least one episode of back strain at some time. Classic presentation is agonizing, lower back pain with a history of lifting a heavy object or making a sudden movement. Pain is increased when bending, lifting, turning, or coughing. Sometimes initial pain is so severe that any movement of the torso is difficult.

Physical exam usually shows guarding of movement due to pain and no true muscle weakness or neurologic deficit. Straight leg raises do not cause pain. This is a clinical diagnosis. Know that imaging does not assist in diagnosis of or treatment for muscle strain.

Most get better quickly: 40% in 1 week, 90% in 2 months. With acute back strain, continuing ordinary activities as tolerated leads to a more rapid recovery than bed rest. Surgery is usually not required; studies show that in non-emergent patients initially considered surgical candidates, conservative treatment is just as effective as surgery in the long term.

Disk Herniation

Herniation presents with local or radicular pain—and with weakness, if severe. Herniated disks are most common at L5/S1 because of progressive thinning of the posterior longitudinal ligament. Central disk herniation can cause saddle pain, anesthesia, and/or incontinence. Classic disk pain is worse when sitting or bending and better when standing or lying.

On exam, patients have pain when performing straight leg raises. MRI without contrast is the test of choice for diagnosing a symptomatic herniated disk.

Long-term outcomes comparing surgery and conservative management are equivalent. Neurologic deficits or intractable pain are indications for surgery (i.e., microdiscectomy). See the Neurology section, Book 5, for more discussion of disk disease.

Spondylolysis and Spondylolisthesis

Spondylolysis is a defect in the isthmus of the neural arch (pars interarticularis) of the 5th (rarely the 4th) lumbar vertebra. This loss of bony continuity is visible, especially on the oblique view of a lumbar x-ray film.

Although it was formerly thought to be congenital, spondylolysis is now thought to be more likely secondary to a stress fracture during childhood.

These patients are more susceptible to spondylolisthesis—a spontaneous subluxation (usually forward) of one lumbar vertebra over another (usually anterior subluxation of L4 over L5). Occasionally, spondylolisthesis results in sciatica, but usually it does not affect the nerves of the cauda equina.

Quick Quiz

- Name another disease that must be considered in a patient with plantar fasciitis.
- What diagnosis should you consider in injection drug users who present with pain in their buttocks?
- Which patients should get urgent imaging of the spine if they present with lumbago?

Spinal Stenosis

Spinal stenosis (aka neurogenic claudication) is discussed in the Neurology section, Book 5. The stenosis of the spinal canal in the lumbar region may cause a crimping or claudication-like symptom due to nerve compression of the cauda equina. Symptoms typically consist of a progressively severe, heavy, aching sensation in the lower extremities after walking or standing several minutes. Symptoms of spinal stenosis worsen with back extension (descending stairs) and improve with back flexion (ascending stairs). Disc herniation is the opposite. This entity must be distinguished from ischemic claudication, which presents as pain with ambulation classically relieved with rest and associated with obvious vascular disease on examination (e.g., bruits, lower extremity hair loss, poorly palpable pulses).

Pain in the SI joint area is not common and may be due to a spondyloarthropathy. Much less commonly, OA can cause pain in the SI area due to lumbar facet joint arthritis, and TB is also a cause (especially in developing countries). Think about infectious sacroiliitis in an injection drug user who presents with buttock-area pain.

Spinal stenosis is usually treated conservatively (i.e., analgesics, physical therapy). Surgery is recommended (most commonly a decompression laminectomy) if symptoms are severe or haven't responded to more conservative measures.

General Approach to Lower Back Pain

Evidence-based practice guidelines issued by the American College of Physicians in 2007, and updated in 2011, focus on stratifying patients with back pain, based on an initial assessment of historical risk factors for cancer/systemic disease ("red flags") and exam evidence of neurologic deficits.

Nonspecific lower back pain is diagnosed when the patient gives the classic history and has no red flags to suggest a more serious etiology. Treat with education (e.g., early mobility and heat application) and analgesics of "proven benefit" = acetaminophen +/– NSAIDs.

Only patients who have neurologic deficits or a "serious" underlying condition (e.g., cancer) should receive urgent imaging. Others should be treated conservatively for 1 month and then should receive reassessment, with imaging reserved for refractory pain.

Underlying conditions that indicate a need for urgent imaging:

- Known cancer diagnosis
- Multiple risk factors for cancer
- Risks for osteomyelitis: injection drug users, +TB screening test, recent TB exposure
- Urinary retention
- Fecal incontinence
- Progressive motor weakness

By imaging, you are ruling out:

- Disk herniation
- Spinal stenosis
- Compression fracture

FOR FURTHER READING

LABS

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